

# RANDOMISED CONTROLLED TRIALS OF ATTENTIONAL BIAS RETRAINING IN SMOKERS

by

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## **ABSTRACT**

Smokers attend preferentially to smoking-related cues in the environment, known as attentional bias. Evidence suggests that attentional bias is related to craving and relapse. Attentional retraining (AR) procedures have been used in laboratory studies to modify attentional bias and processes related to drug use, but investigations on the clinical value of AR in addiction are scarce. This thesis reports on two randomised controlled trials investigating the efficacy of AR with modified visual probe tasks in smokers. The first study explored the effects of varying the length of AR on attentional bias, craving, mood and withdrawal in current smokers. No retraining effects were observed after either a short, medium or long block of AR. The second study explored the efficacy of AR on attentional bias and smoking cessation outcomes in treatment-seeking smokers. While AR procedures were feasible to deliver within smoking cessation clinics, the intervention did not significantly reduce attentional bias, craving, withdrawal symptoms or the likelihood of relapse. These results and the literature in general show that there is no clear association between attentional bias and craving and relapse. Current AR procedures are not effective in smokers and should not be used in smoking cessation treatments, as they currently stand.

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## ABBREVIATIONS

Abbreviation	Term
AACTP	Alcohol Attention-Control Training Program
AB	Attentional bias
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Attentional retraining
BCHCT	Birmingham Community Healthcare Trust
BEN	Birmingham East and North (PCT)
CI	Confidence interval
CO	Carbon monoxide
DoH	Department of Health
EMA	Ecological momentary assessment
fMRI	Functional magnetic resonance imaging
FTND	Fagerström Test of Nicotine Dependence
GP	General practice
HoB	Heart of Birmingham (PCT)
HR	Hazard ratio
LES	Local Enhanced Service
M	Mean
mg	Milligrams
mm	Millimetre
MPSS	Mood and Physical Symptoms Scale
MPSS-C	Mood and Physical Symptoms Scale-Craving (combined)
MPSS-M	Mood and Physical Symptoms Scale-Mood (combined)
ms	Milliseconds
NCSCCT	National Centre for Smoking Cessation and Training
NHS	National Health Service
NRT	Nicotine replacement therapy
OR	Odds ratio
PCT	Primary Care Trust
ppm	Parts per million
PT	Placebo training
QSU-Brief	Questionnaire on Smoking Urges-Brief
RR	Risk ratio
RPI	Relapse prevention intervention
RT	Reaction time
SB	South Birmingham (PCT)
SD	Standard deviation
SOA	Stimulus onset asynchrony
SSS	Stop smoking services
STAI-State	State-Trait Anxiety Inventory state (subscale)
STAI-Trait	State-Trait Anxiety Inventory trait (subscale)
SUSAR	Suspected unexpected serious adverse reaction
VAS	Visual analogue scale
VP	Visual probe task
Wt	Walsall Teaching (PCT)

## CHAPTER 1: INTRODUCTION

### 1.1 Smoking cessation context

Tobacco smoking remains a major cause of many preventable diseases and premature death, killing an estimated 102,000 people in 2009 in the UK alone (Peto et al., 2012). Since the publication of the UK government's White Paper, *Smoking Kills* (Department of Health, 1998), which put forward a tobacco control strategy to tackle and reduce smoking prevalence, the incidence of smoking has steadily declined in England over the past decade, from 27% in 2000 to 20% in the present day (Office for National Statistics, 2012). Contributing factors to this decline include an advertising ban on tobacco products, smoke-free legislation prohibiting smoking in enclosed work and public places and treatments provided by a network of National Health Service (NHS) Stop Smoking Services (SSS).

The NHS SSS, which were rolled out across the UK in 2000 after being piloted in deprived areas, offers both cost-effective and evidence-based smoking cessation treatments. Since its implementation, a reported four million people have set a quit date with the SSS, of which two million have stopped smoking for at least four weeks (Department of Health, 2010). Despite these short-term success rates, approximately 75% of initially successful 4-week quitters relapse [defined here as a return to regular smoking (Hughes et al., 2003)] within one year of quitting, with relapse occurring most commonly

in the first six months after cessation (Judge et al., 2005). Interventions designed to prevent relapse may therefore be key to improving longer-term cessation rates.

### ***1.1.1 Current provision of smoking cessation and relapse prevention treatments within the NHS SSS***

The NHS SSS offer a routine stop smoking programme supporting service-users up to 12 weeks during any given quit attempt. Health care practitioners are trained to support service-users with evidence-based guidelines for smoking cessation (National Centre for Smoking Cessation and Training, 2011). Effective components of the programme include the provision of weekly behavioural support (Lancaster & Stead, 2005) and pharmacotherapy in the form of nicotine replacement therapies [NRT - gum, lozenge, transdermal patch, nasal spray, mouth spray, inhalator and sublingual tablet (Stead et al., 2008)], varenicline (Cahill et al., 2012) or bupropion (Hughes et al., 2007).

There is currently no guidance on providing relapse prevention interventions (RPIs) in the SSS, on top of what is routinely offered as cessation treatment in stop smoking programmes (RPIs are defined here as any treatment designed to reduce rates of relapse to smoking at any point after quit day, in addition to that of standard cessation treatment). A survey of SSS managers revealed that RPIs had been offered by some services despite limited evidence of efficacy at the time the survey was administered (Agboola et al., 2010a). A Cochrane review of relapse prevention trials in smoking cessation found insufficient evidence to support the use of behavioural methods to prevent relapse for



individuals achieving initial abstinence and only weak evidence in favour of using some pharmacotherapies when provided for an extended period of time after short-term abstinence had been achieved (Hajek et al., 2009). However, a recent updated review which stratified interventions by content, included abstinent smokers only and had a stricter criterion on the synthesis of follow up time-points across studies, found that behavioural self help interventions appear to be effective in preventing relapse in initially unaided quitters and pharmacotherapies increase long-term abstinence in abstinent smokers, but not behavioural support (Agboola et al., 2010b). Of particular note is that all included studies in the review consisted of RPIs involving pharmacotherapy, self-help and/or counselling only, which are predominantly extensions of what is already available during the initial phases of treatment. It appears as though other approaches have not been studied as extensively; in the following sections I shall present evidence to suggest the use of more novel approaches to relapse prevention in the context of what is known about the relapse process, and the emerging prominence of the role of implicit cognitions in models of relapse prevention.

## **1.2 The relapse process**

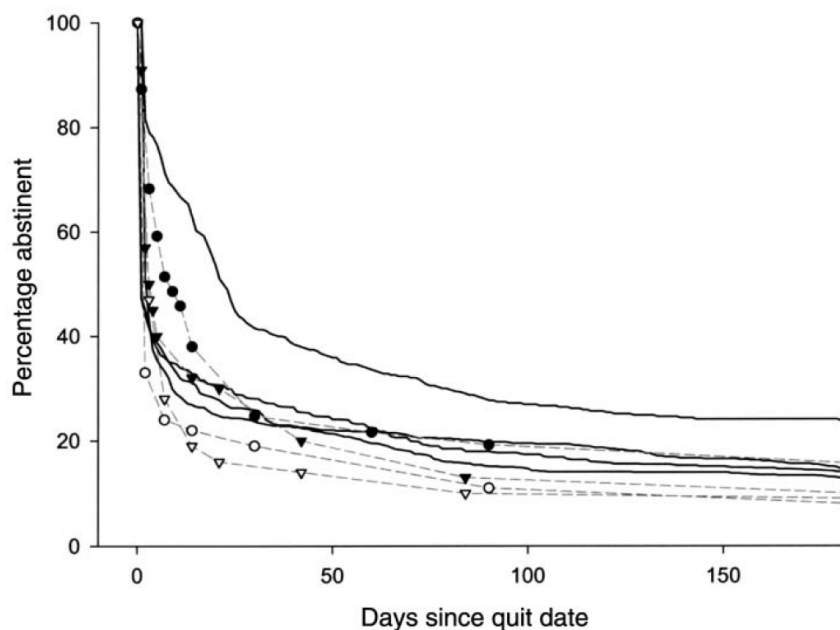
### ***1.2.1 Relapse and abstinence curves for untreated and treated smokers***

Despite the vast amount of empirical work to date on the study of relapse in addiction, the factors contributing to the relapse process are not yet fully understood. We understand that upon initiation of any given quit attempt, the likelihood of a lapse (defined here as a slip or an incident of smoking, followed by continuation of the quit attempt) occurring after an initial period of abstinence is high and has been shown to predict whether or not a

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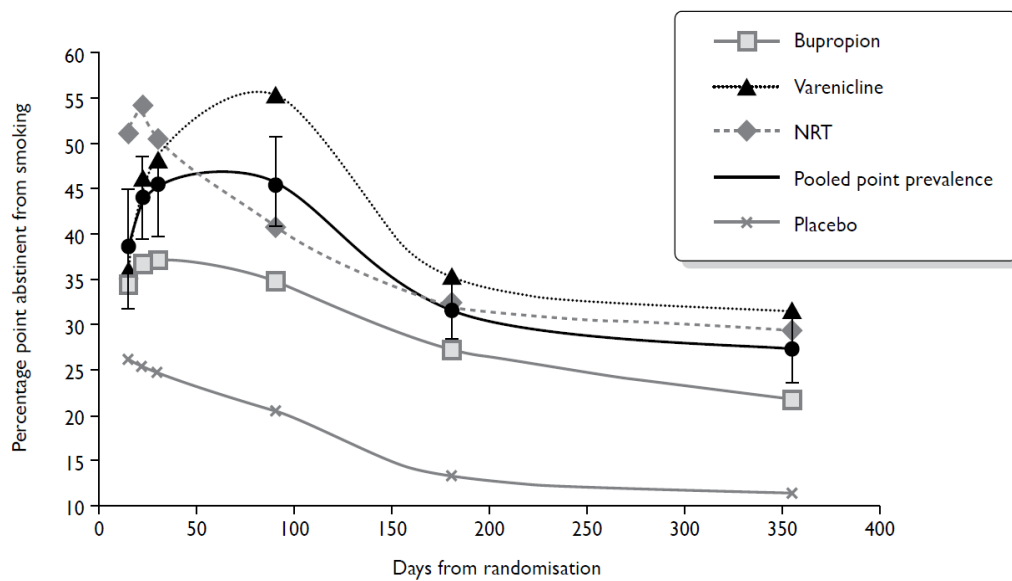
smoker will achieve abstinence in the longer-term (Kenford et al., 1994). It remains difficult, nevertheless, to ascertain why or identify when a lapse occurs and the nature by which it translates into full relapse to smoking.

Patterns of relapse have been depicted in relapse curves derived from survival analyses of untreated smokers (Hughes et al., 2004a). Where ‘survival’ is defined as abstinence from smoking, the shape of the curve reflects the number of smokers still abstinent over time. In the general untreated population, the majority of smokers return to smoking within the first eight days of a quit attempt; thereafter, most relapses occur within three months of quitting (Figure 1), leaving only 3-5% abstinent at six months (Hughes et al., 2004a).



**Figure 1. True survival curves (solid lines) and line graph relapse curves (dotted lines) in self-quitters, taken from Hughes et al., 2004a**

Preliminary evidence from abstinence curves of smokers treated with pharmacotherapy (NRT, bupropion or varenicline) and behavioural support suggests that such treatments delay relapse in comparison to smokers who receive no cessation support [Figure 2 (Coleman et al., 2010)]; for NRT, the trajectory mimics the curve for untreated smokers where abstinence rates are highest at the onset of the quit attempt although a steadier decline in abstinence is observed in comparison thereafter. For bupropion, abstinence rates are fairly constant throughout. For varenicline, the rate appears to increase within the first three months and decelerates after this point. The similarity in the late slope pattern for each treatment suggests that there is very little difference between treatments beyond three months and highlights the comparable decline in abstinence, with varenicline producing a higher proportion of abstinent smokers overall at 12 months (31%) in comparison to NRT (29%) and bupropion (22%). Thus, treatment effects observed early on in a quit attempt seem to have small incremental effects on the proportion of smokers who remain abstinent in the longer-term, although the rate of relapse after the initial treatment period does not vary across treatments.



**Figure 2. Abstinence curves (shown as line graph) in treated smokers, taken from Coleman et al., 2010. Horizontal lines indicate the 95% CIs for the combined medications estimate at each pre-specified follow-up**

Piasecki et al. (2002) distinguished the early and late components of the relapse curve by coining two distinct phases: a ‘cessation attempt’ period to signify the initial attempt to stop smoking and a period of ‘relapse susceptibility’ to delineate later relapses in the process. The authors suggest that a true, effective RPI should produce significant effects in the relapse susceptibility phase by reducing the likelihood of later lapses. This would be illustrated on a relapse curve by a uniform slope with a slower decline in abstinence rates over time but the preliminary evidence above suggests that current smoking cessation treatments do not achieve this. To reduce the probability of relapse in these later stages, it is important to first consider the factors that potentially influence the relapse process so that more targeted approaches to relapse prevention can be developed. In the following section, I describe some of these factors including the role that implicit cognitions might play in the relapse process.

### ***1.2.2 Relapse as a dynamic process***

Most theoretical accounts of smoking relapse focus on specific mechanisms of drug motivation, the most widely studied in the field being Marlatt and Gordon's (1985) cognitive-behavioural model of relapse, which forms the basis of many RPIs in smoking cessation (Hajek et al., 2009). The original model proposes that relapse centres on 'high risk situations' and how individuals respond to these situations (Marlatt & Gordon, 1985). High risk situations include internal (e.g. emotional states such as negative affect) and external (e.g. environments where smokers are present) contexts that increase an individual's vulnerability to engaging in a target behaviour (Hendershot et al., 2011). Whether lapses or relapse occurs depends primarily on the individual's ability to cope with high-risk situations. The relapse prevention approach developed from this model therefore involves skills-based training, designed to encourage individuals to identify high-risk situations and develop coping strategies to reduce the likelihood of relapse occurring.

The model has since been reformulated in light of numerous developments in empirical studies that recognise relapse as a dynamic process involving complex interactions, rather than being static and time-invariant (Witkiewitz & Marlatt, 2004). Arguably, much of the research on relapse in the last decade has focused on individual differences, enduring traits or characteristics that lead to relapse. For example, being younger, smoking more cigarettes a day, having lower self-efficacy at the point of quitting are contributing factors (Ockene et al., 2000).

The reformulated cognitive-behavioural model of relapse recognises both tonic processes that are stable (e.g. personality) and phasic responses which are transient (e.g. urges and mood that can vary over time and contexts) that interact with each other to predict relapse risk (Witkiewitz & Marlatt, 2004). Recent empirical studies reveal the complexity of the relationship of each construct to relapse in light of new methodologies like Ecological Momentary Assessment (EMA) which focus on real-time data collection in real-world environments (Shiffman et al., 2008). EMA methods have been used to capture temporal variations in factors associated with relapse; for example, one study found that participants exhibited lower self-efficacy on the day prior to a lapse and on subsequent days lower self-efficacy was associated with progression to relapse (Shiffman et al., 2000). The intensity of daily urge to smoke has been found to predict smoking lapse on the following day (Van Zundert et al., 2012; Shiffman et al., 1997). Negative affect has been found to rise in the hours preceding a lapse, but not in the days prior to it (Shiffman & Waters, 2004a). Other components of the model have also received support from EMA studies, including self-control and coping (Shiffman et al., 1996) and smoking outcome expectancies (Gwaltney et al., 2005).

Other factors of the model have received less emphasis until now. Emerging out of expectancy research is an increasing interest in the influence of implicit cognitive processes on our understanding of dynamic relapse processes (Stacy & Wiers, 2010). Implicit cognitions are defined as processes (e.g. attentional bias) that often occur automatically and can be inferred indirectly from other behaviours (e.g. measures of reaction time as described in section 1.3.2). In contrast to explicit cognitions - which

focus on the assumption that addictive behaviours are borne out of rational decision making - implicit cognitions are described as impulsive and lead to relatively automatic drug use in response to drug-related cues. Implicit measures of cognitive processes have been found to be correlated with relapse outcomes across several addictive behaviours, including alcohol (Cox et al., 2002), heroin (Marissen et al., 2006) and smoking [(Waters et al., 2003a) see section 1.5 for full description]. Central to this thesis and thus the focus of the discussion in the following sections is a closer examination of implicit cognitive processes, namely attentional bias and its theoretical basis, how it might relate to the relapse process and its potential as a target for preventing relapse in smokers who are attempting to quit.

### **1.3 Attentional bias**

#### ***1.3.1 Theoretical background***

When drug users show excessive attention towards drug-related cues in the environment, they are said to exhibit what is known as an ‘attentional bias’. It has most often been explained by theories that endorse the tenets of classical conditioning. Robinson and Berridge’s (1993) incentive-sensitization theory proposes that through repeated drug-use, the dopaminergic response produced by the reward system in the brain becomes sensitized and increases the salience of cues related to drug-use. Through Pavlovian learning, these drug-related cues become associated with drug-related rewards, even in the absence of the drug itself. As a consequence, drug-related cues appear appealing to a drug-user, ‘grab’ their attention and becomes ‘wanted’ to the extent that their behaviour may be guided towards drug use (Robinson & Berridge, 1993). Cigarette smokers have

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been reported to attend differentially to environmental cues or ‘stimuli’ by exhibiting an attentional bias or readiness to process smoking-related stimuli over others, triggered by the motivational properties associated with such stimuli (Robinson & Berridge, 1993; Robinson & Berridge, 2001). Studies that support the incentive-sensitization theory show that drug-users respond with greater activation in brain reward circuitry when exposed to drug-related stimuli in comparison to non-drug users (see Wilson et al., 2004 for a review of studies). Using functional neuroimaging techniques (Janes et al., 2010), smoking-related stimuli have been shown to evoke greater activation in the mesolimbic reward circuit than neutral cues in smokers, while non-smokers show no differential response in activation to either stimulus-type (Rubinstein et al., 2011).

Like attentional bias, subjective cravings or urges to smoke are also perceived as an output of the sensitized reward system according to the incentive sensitisation theory. More recent models (Franken, 2003; Ryan, 2002) propose that attentional bias for drug-related cues and subjective craving may have a mutual excitatory relationship. Based on this assumption, a cycle ensues when drug-related cues become the focus of attention, craving increases and so the salience of the drug-related cues increase to the point where the drug is used. Moreover, increases in attentional bias are perceived as both a cause and consequence of high levels of craving (Franken, 2007; Franken, 2003). Thus, smokers with high levels of craving may be more likely to search the environment for smoking-related cues or notice them more readily, while prolonged attentional processing of smoking-related cues could lead to an increase in urge to smoke. Kavanagh et al. (2005) suggest in their elaborated intrusion theory that internal states (e.g. withdrawal symptoms,



nicotine deprivation) or external cues (e.g. sight of a cigarette packet) could initiate intrusive thoughts about a drug. Here, the ‘intrusion’ - subjective craving - is elaborated on perhaps by excessive rumination about the experience of craving or by maintaining attentional vigilance on the cues that triggered the thought process. Further discussion on the role of cue-induced cravings is provided in section 1.4.1.

Habit based theorists also regard drug use as automatic and ‘stimulus bound’ (Tiffany, 1990), meaning that the sight of a drug cue has the ability to initiate a chain of action towards a substance. It is only when this chain of action is disrupted, for example, when the drug is unavailable, that craving is experienced. Thus, unlike the causal relationship depicted in Franken’s (2003) model described above, it could be possible that attentional bias leads to the pursuit of a drug, even without the experience of craving.

In contrast to classical conditioning theories that describe the development of attentional bias, the theory of current concerns proposes that cognitive biases develop from the drug users’ general motivational state and their pursuit of a drug (Klinger & Cox, 2004). A drug-related current concern will implicitly bias cognitive processing towards drug-related cues; because the overall goal of a drug user is to obtain their drug of choice, current concerns will prompt users to automatically process drug cues related to this pursuit and will continue to do so until the goal is reached or abandoned (Cox et al., 2006a). Pursuit of a drug is therefore kept in focus by such cognitive biases.

Taken together, the aforementioned theories of attentional bias in addiction all suggest that drug-related cues have the ability to capture attention relatively automatically. Drug-related cues potentially act as a driving force in drug-taking behaviour and so disrupting this process by reducing attentional bias, for example, could hinder the pursuit of a drug. These models also suggest that attentional bias and subjective craving interact with each other and potentially influence drug use. Understanding the nature and significance of this relationship is therefore necessary to understanding how relapse to smoking unfolds, and is one of the central objectives of this thesis. In the following sections, I will discuss what methods have been used to assess attentional bias (section 1.3.2) and what is known already about the relationship between drug-related cues, craving and relapse (sections 1.4 and 1.5).

### ***1.3.2 Attentional bias measures***

Several paradigms have been used to measure cognitive processing biases, either directly (e.g. eye-tracking) or indirectly (e.g. visual probe task). These tasks typically rely on measuring reaction times (RTs) to relevant stimuli to infer the amount of bias exhibited by a participant. Different subcomponents of attention and attentional bias can be examined depending on the type of task used. For example, some tasks measure the rapid orienting of attention, while others measure the maintenance or delayed disengagement of attention (see Field & Cox, 2008, for a review). In the next section, I will outline the most commonly used tasks and focus on the procedures that are most relevant to the research studies described in Chapters 2 and 3.

### *1.3.2.1 The addiction Stroop task*

The modified addiction Stroop task (Cox et al., 2006b), a variant of the classic Stroop task (Stroop, 1935), has been used extensively to measure selective processing of drug-related stimuli (Drobes et al., 2006; Sharma et al., 2001; Waters et al., 2003a). In this task, participants are presented with neutral or drug-related words printed in colour and they are asked to name the colour of the words as quickly and accurately as possible while ignoring the semantic content of the words. Similarly pictorial presentations of drug-related and neutral stimuli are also used in addiction Stroop paradigms (Bruce & Jones, 2004); participants are required to name the colour of the border of pictures presented as quickly as possible while attempting to ignore the content of the pictures. A processing bias towards drug-related stimuli is indicated by slower colour naming of drug-related words/pictures in comparison to neutral words/pictures, suggesting that attention is captured by the meaning of the drug-related words/pictures and performance is thus impaired on the task.

Smokers, in comparison to non-smokers, have been found to exhibit a processing bias for smoking-related stimuli than neutral stimuli (Munafo et al., 2003). Similarly, processing biases have been found in drug-users of other substances in comparison to non-abusers, including alcohol abusers (Cox et al., 2000; Sharma et al., 2001), heroin addicts (Franken et al., 2000), cannabis users (Field et al., 2006) and cocaine addicts (Hester et al., 2006).

There is some ambiguity over the mechanisms underlying the Stroop effect, which is why this is referred to as a ‘cognitive processing bias’ rather than an attentional bias in this discussion. This is because there are alternative interpretations for why the interference occurs and different mechanisms at play, which could give rise to the same observed interference. For example, attempts to avoid drug-related stimuli [termed cognitive avoidance in anxiety literature (Deruiter & Brosschot, 1994)] may also result in the slower colour-naming of drug-related words. This has been demonstrated in a study where abstinent alcoholics showed increased Stroop interference when they were told to suppress their thoughts about alcohol, in comparison to those who were not encouraged to do so (Klein, 2007). An interpretation of the Stroop effect therefore requires careful consideration; I herein refer to this effect as a processing bias throughout this thesis.

The addiction Stroop task is likely to measure the maintenance or delayed disengagement of attention rather than the rapid orienting of attention. Evidence for this comes from ‘carryover’ effects noted across addiction Stroop studies (Cane et al., 2009). Carryover effects have been found where colour naming performance is impaired on trials of neutral stimuli that have been presented immediately after trials of drug-related stimuli; smokers have been found to respond slower to words that appear after smoking-related words than after neutral words (Waters et al., 2003b). Thus, this slow down in cognitive processing which carries over into subsequent trials suggests that there might be a rumination effect on drug-related stimuli that is likely to reflect a difficulty in disengaging attention.

### *1.3.2.2 The visual probe task*

Another widely used measure of attentional bias is the visual probe task (MacLeod et al., 1986). In this task, participants are presented with stimuli consisting of a pair of words or pictures that are presented side by side on a computer screen. One stimulus is neutral (e.g. a picture of a man holding a pen) and the other is related to smoking (e.g. a picture of a man holding a cigarette). After a short interval, the picture pairs disappear and are replaced by a single probe stimulus (e.g. a square or triangle) that appears in the location formerly occupied by one of the pictures. The probe stimulus replaces the neutral and smoking-related pictures with equal frequency. Participants are then required to press either the up arrow or down arrow on the computer keyboard to indicate which picture has been replaced as quickly as possible in response to the probe.

Based on the principle that detection of the probe is quicker in the location in which the participant is already fixated, a participant who has an implicit bias towards smoking will presumably be looking in the direction of the smoking-related stimuli on the outset.

Attentional bias towards smoking is indicated by faster RTs to the probe that appears in the location of the smoking-related picture rather than the neutral picture. Smokers, but not non-smokers have demonstrated an attentional bias for smoking-related pictorial cues (Bradley et al., 2004; Ehrman et al., 2002). Other drug users have shown an attentional bias towards drug-related stimuli of their choice; for example, cannabis users have shown faster approach responses towards cannabis-related pictorial cues than neutral cues (Field et al., 2006).

Different stimulus presentation times are assumed to measure different components of attentional bias on the visual probe task. The stimulus onset asynchrony (SOA), which is the time in which a picture is presented on a computer screen in each trial, has been manipulated in visual probe task studies to investigate the initial orienting of attention or speeded detection of drug-related stimuli versus the maintenance or delayed disengagement of attention. Short SOAs, typically less than 200 milliseconds (ms), are likely to reflect early processes while longer SOA durations of between 500 ms and 2000 ms reflect later slower processes. This is based on the assumption that only one shift in attention seems plausible when two stimuli are presented at an SOA duration of less than 200 ms, while multiple shifts are possible at SOAs of over 500 ms (Field & Cox, 2008). Accordingly, shorter SOAs may indicate the rapid initial orienting of attention while longer SOAs may reflect maintenance or disengagement of attention; this line of reasoning is generally accepted in the anxiety literature (Koster et al., 2004).

The differentiation between the two subcomponents has been best measured by combining the visual probe paradigm with eye-tracking methodology. As the visual probe task is limited to measuring the allocation of attention at the time of stimulus offset, eye-tracking allows for the measurement of attention over the duration of stimulus presentation. Thus, eye-tracking methodology provides a more direct measurement of both initial orienting and delayed disengagement. Attentional bias is inferred from eye movements, for example by measuring the direction of first eye movements or the amount of time individuals maintain their gaze on drug-related stimuli versus neutral stimuli (also known as ‘dwell time’). In a study of heavy drinkers (Schoenmakers et al., 2008) and

cannabis users (Field et al., 2006), attentional bias RTs on the visual probe tasks were positively correlated with gaze dwell times when drug-related stimuli were presented for 2000 ms, which lends support to the notion that longer presentation times capture the maintenance of attention. Similarly, smokers have a higher proportion of first eye movements and a longer dwell time towards smoking-related stimuli than neutral stimuli (Field et al., 2004; Mogg et al., 2003). Furthermore, smokers have been found to direct their gaze towards dynamic smoking-related cues more quickly, more often and for a longer duration in comparison to non-smokers (Lochbuehler et al., 2011).

Arguably, these two subcomponents of attention may have state-like or trait-like qualities. Faster attentional processes like the initial orienting of attention may be indicative of a trait that has developed after years of conditioning to smoking cues and accordingly, may have a consistent presence in certain drug users. On the other hand, the maintenance of attention may be regarded as a state-like construct and may be influenced more so by motivational factors such as craving (LaBerge, 1995). Biases in maintained attention may therefore be more evident in situations of high cravings, for example when smokers are nicotine deprived. Although this is somewhat speculative, these trait-like and state-like features of attentional bias may be important when examining the relationship between attentional bias and craving.

In summary, both Stroop and visual probe task paradigms have been used to demonstrate that smokers show cognitive processing biases towards smoking-related stimuli compared

to non-smokers. It is likely that each task taps into different subcomponents of attention; the Stroop task is likely to measure the maintenance or delayed disengagement of attention while the visual probe task appears to capture both initial orienting and delayed disengagement of attention, depending on the duration of stimulus presentations. Both of these tasks were used in the research studies described in Chapters 2 and 3.

#### **1.4 Attentional bias and craving: are they related?**

In section 1.2.2, I highlighted that attentional bias and craving feature in recent models of relapse and in section 1.3.1, I discussed how several theoretical models predict that attentional bias is associated with subjective craving. Here, I introduce how this relationship has been investigated in addiction and what is known so far.

Firstly, it is important to distinguish between two types of craving reported in the addiction literature: background craving and episodic or cue-induced craving.

Background craving perpetuates throughout the day as a steady, tonic state and reduces over time while episodic craving – which typically overlays background craving – occurs during bouts of intense craving and is usually triggered by situational cues, for example exposure to smoking cues or alcohol consumption (Ferguson & Shiffman, 2009; Marlatt & Gordon, 1985; Niaura et al., 1988; Shiffman, 1982). Some authors propose that background craving and episodic craving arise from separate processes (Carter et al., 2009). For the purpose of composition, I predominantly refer to and focus on episodic



craving as the majority of studies mentioned below have most commonly investigated attentional bias in relation to cue-induced cravings.

The theories proposed by Franken (2003) and others suggest that there is a reciprocal relationship between attentional bias and craving. One way to examine this relationship is to experimentally manipulate either craving or attentional bias in order to produce a corresponding effect, such that an increase in craving would result in an increase in attentional bias and vice versa. This causal relationship has been studied across several substances using experimental manipulations like cue exposure (Tiffany & Drobes, 1990) or attentional retraining procedures (Attwood et al., 2008) which are described below. Other experimental manipulations include priming (Schoenmakers et al., 2008), negative mood induction (Bradley et al., 2007) and deprivation (Waters & Feyerabend, 2000) all of which are described in Field and Cox's (2008) review.

It is worth noting that there are methodological differences across these studies which complicate the study of this association. Studies typically vary according to the attentional bias tasks used (e.g. visual probe task versus Stroop task), the samples used (e.g. treatment-seeking versus non-treatment seeking, light users versus heavy users), the type of substance abusers tested (e.g. cigarette smokers, alcohol users, cocaine addicts) and the measures of craving used (e.g. single item versus multi-item questionnaires). Taking account of this, a recent meta-analysis of 68 studies found a significant, although somewhat weak ( $r=0.19$ ), positive correlation between the magnitude of attentional bias

and the strength of craving across users of various substances (Field et al., 2009a). In the sections that follow, I discuss some of the empirical studies that have attempted to elucidate the relationship between attentional bias and craving. I focus namely on studies that used experimental manipulations like cue exposure and attentional retraining, as they are most relevant to the studies described in Chapters 2 and 3.

#### ***1.4.1 Cue-induced craving manipulations***

In cue-reactivity research, drug-related stimuli are known to produce increases in subjective craving and physiological arousal (Carter & Tiffany, 1999). One of the most commonly used procedures to evoke craving in smoking studies involves exposure to smoking-related stimuli (Carter & Tiffany, 2001; Tiffany & Drobes, 1990), which can consist of either in vivo cues (e.g. holding a lit cigarette), imagined cues (e.g. imagining holding a lit cigarette) or images of smoking paraphernalia (e.g. a short film of people smoking). For example, Field et al. (2007a) demonstrated that both subjective craving and processing biases for smoking-related stimuli could be increased after smokers were presented with a smoking cue (a lit cigarette) in a smoking environment than a control cue (a pen) in a neutral environment. The study also showed that the corresponding effect on attentional bias was mediated in part by cue exposure effects on subjective craving.

More recently, neuroimaging studies have helped establish patterns of brain activation associated with cue exposure, attentional bias and craving. In a study by Kang et al. (2012) temporarily-abstinent smokers were exposed to smoking-related and neutral visual

cues while undergoing functional magnetic resonance imaging (fMRI) to study changes in brain reactivity and eye-tracking to measure attentional bias, followed by a measure of craving using the Questionnaire on Smoking Urges-Brief (QSU-Brief). Smokers showed significantly longer gaze dwell times in response to smoking-related cues than neutral cues, indicating an attentional bias towards smoking cues. Attentional bias was also positively correlated with QSU-Brief scores in which higher craving was associated with greater processing of smoking-related cues. Furthermore, attentional bias to smoking cues was associated with greater activation in regions of the brain linked to the mesolimbic reward system and visuospatial attention; subjective craving was associated with heightened activation in areas engaged in reward-related decision-making and cognitive control, which lends support to incentive salience theories in addiction (Franken, 2003; Robinson & Berridge, 2001).

#### ***1.4.2 Attentional bias manipulations***

Other studies have investigated the effect of manipulating attentional bias on subjective craving to test a causal association. If increases in craving increase attentional bias, then it should be demonstrable that increases in attentional bias lead to increases in craving if there is a reciprocal relationship. Attentional retraining (AR) procedures – where standard attentional bias tasks are modified to manipulate attentional bias – have been used in train-to-attend and train-to-avoid experimental manipulations. The most common AR procedure used in substance-related studies is a modified visual probe task which has shown that individuals with specific drug use patterns are able to increase or decrease attentional bias towards their drug of choice (Attwood et al., 2008; Field & Eastwood,

2005; Field et al., 2007b; Field et al., 2009b; McHugh et al., 2010; Schoenmakers et al., 2007). In the train-to-attend manipulation, the probe replaces the drug-related stimuli more frequently than the neutral stimuli; by comparison in the train-to-avoid manipulation, the probe replaces the neutral stimuli on a greater number of occasions. Consequently attention is trained towards one particular stimulus type.

In addiction retraining studies, the effects of AR on subjective outcomes (e.g. craving) and behavioural outcomes (e.g. drug consumption) have been investigated. These have mainly been laboratory studies in alcohol users and more recently tobacco users trained using a modified visual probe task. Table 1 displays the characteristics of all the published addiction retraining studies available at the time of writing. The first of these studies found that social drinkers who were trained to attend to alcohol-related stimuli showed increases in attentional bias for alcohol-related stimuli; these changes were also associated with increases in urge to drink and actual beer consumption during a post-task taste test (Field & Eastwood, 2005). Conversely, those who were trained to avoid alcohol-related stimuli showed reductions in attentional bias for alcohol-related stimuli and consumed less beer than the comparison group, but no changes in urge to drink were observed. Field et al. (2007b) replicated this study with the inclusion of a control group and found the predicted direction of change in attentional bias in the two experimental groups, as well as no change in attentional bias in the control group. Alcohol craving increased among participants in the attend group, but only for those who were aware of the experimental contingencies, i.e. participants who reported the relationship between the location of the probe and stimulus-presentation correctly in a post-task questionnaire. However in

contrast to the findings of the earlier study, there were no differences between groups in the volume of beer consumed. Schoenmakers et al. (2007) carried out a similar study where heavy social drinkers had learned to avoid alcohol-related stimuli and develop an attentional bias towards soft drinks, although the authors reported that training had no effect on post-task craving or drink choice.

At the time of writing, only three laboratory studies reported outcomes for AR in current cigarette smokers (Attwood et al., 2008; Field et al., 2009b; McHugh et al., 2010).

Attwood et al. (2008) found that AR increased attentional bias in participants who were trained towards smoking-related stimuli and decreased attentional bias in those trained towards neutral stimuli. Furthermore, when participants were measured on their response to a lit cigarette following the training procedure, greater increases in subjective craving were found in male participants who attended to smoking-related stimuli than those trained towards neutral stimuli. However, no effect of training on smoking topography (e.g. number of puffs taken, puff duration, etc.) was observed. Field et al. (2009b) and McHugh et al. (2010) replicated this study with the inclusion of a control group. Field et al. (2009b) found that attentional bias was greater after training in the attend group than the avoid and control groups, but these effects disappeared after one day. Neither the train-to-attend or train-to-avoid manipulations had any effect on urge to smoke, although unlike in the Attwood et al. (2008) study, no cue exposure task was used. Additionally, no group effects of retraining on motivation to smoke were observed. McHugh et al. (2010) compared an avoid group with a control group and found no change in attentional bias

and no effects of retraining on subjective craving. Unlike the Attwood et al. (2008) and Field et al. (2009b) studies, no behavioural measures of tobacco seeking were taken.

While the relationship between attentional bias, subjective craving and behavioural outcomes is currently equivocal, it is important to note that inconsistencies across the above studies may be due to procedural differences in design. For example, across the alcohol retraining studies, the number of training trials varied from 600 trials to 960 trials while in the tobacco retraining studies, the number of trials ranged from 512 to 896. It is therefore unclear whether retraining effects on attentional bias, craving and drug-taking were contingent on the amount of retraining delivered. Chapter 2 describes a study in which we explored varying the length of AR on these particular outcomes.

**Table 1. Characteristics of tobacco and alcohol-related attentional retraining studies. AB=attentional bias**

Author	Type of retrained substance cue	Sample (N)	Treatment seeking?	Groups	Type of task	No. of retraining trials	No. of test trials	Effect on cognitive bias	Untrained stimuli	Alternative task measure	Effect on subjective outcome measure	Effect on behavioural outcome measure
Field et al. (2005)	Alcohol	Heavy social drinkers (n= 40)	No	Attend & Avoid	Visual probe task	896	56	Attend: Increased AB Avoid: Decreased AB	N/A	N/A	Attend: Increased urge to drink only on one measure Avoid: No effect	Attend group consumed more alcohol than avoid group during taste test
Field et al. (2007b)	Alcohol	Heavy social drinkers (n= 60)	No	Attend, Avoid & Control	Visual probe task	960	120	Attend: Increased AB Avoid: Decreased AB (approached significance) Control: No change	Attend: Increased AB Avoid: Increased AB Control: No change	No	Attend: Increased urge to drink only in participants aware of experimental contingency Avoid: No effect on urge to drink	No effect on alcohol consumption during taste test in any group
Schoenmakers et al. (2007)	Alcohol	Heavy social drinkers (n=106, males)	No	Avoid & Control	Visual probe task	600	48	Avoid: Decreased AB Control: No change	No	No	Avoid: No effect on urge to drink Control: No effect on urge to drink	No effect on drink preference in any group

Table 1 continued

Author	Type of retrained substance cue	Sample (N)	Treatment seeking?	Groups	Type of task	No. of retraining trials	No. of test trials	Effect on cognitive bias	Untrained stimuli	Alternative task measure	Effect on subjective outcome measure	Effect on behavioural outcome measure
Attwood et al. (2008)	Tobacco	Current smokers (n=55)	No	Attend & Avoid	Visual probe task	512	128	Attend: Increased AB Avoid: Decreased AB	N/A	N/A	Attend: Increased urge to smoke across cue exposure, only in male participants aware of experimental contingency (this approached significance only on one measure) Avoid: No effect on urge to smoke	No effect on smoking topography
Field et al. (2009b)	Tobacco	Current light smokers (n=72)	No	Attend, Avoid & Control	Visual probe task	896	160	Attend: Increased AB Avoid: Decreased AB (approached significance) Control: No change	No	No	Attend: No effect on urge to smoke Avoid: No effect on urge to smoke Control: No effect on urge to smoke	No effects on motivation in any group



Table 1 continued

Author	Type of retrained substance cue	Sample (N)	Treatment seeking?	Groups	Type of task	No. of retraining trials	No. of test trials	Effect on cognitive bias	Untrained stimuli	Alternative task measure	Effect on subjective outcome measure	Effect on behavioural outcome measure
Fadardi & Cox (2009)	Alcohol	Social drinkers (n=40) Hazardous drinkers (n=89) Harmful drinkers (n=92)	Yes	Avoid only	Stroop task	Goal directed training set by participant 2 full sets of training in one session (duration of approx. 1 hour) 2 sessions (social & hazardous drinkers), 4 sessions (harmful drinkers)	192	Decrease in cognitive bias across all groups; significant reduction in hazardous and harmful drinkers vs. social drinkers	N/A	N/A	N/A	Harmful drinkers: significant reduction in weekly alcohol consumption from baseline to post-training and reduction maintained at 3 month follow-up
Schoenmakers et al. (2010)	Alcohol	Alcohol-dependent patients (n=43)	Yes	Avoid & Control	Visual probe task	528 (total of 2640 across 5 sessions)	96	Avoid: Decreased AB Control: No change	Avoid: Smaller bias than control	N/A	Avoid: No effect on urge to drink Control: No effect on urge to drink	Time to relapse longer in avoid vs. control group Earlier discharge from facility in avoid vs control group
McHugh et al. (2010)	Tobacco	Current smokers (n=64)	No	Avoid & Control	Visual probe task	560	96	Avoid: No change Control: No change	No (only novel stimuli used)	N/A	Avoid: No effect on urge to smoke Control: No effect on urge to smoke	N/A

To recapitulate, there is some evidence to suggest that attentional bias is related to craving, although correlations are weak (Field et al., 2009a). Laboratory studies have used procedures like cue exposure and attentional retraining to investigate this causal association by experimentally increasing craving or manipulating attentional bias. Evidence from AR studies in non-treatment seeking substance-users demonstrates that increases and decreases in attentional bias are plausible but are not always consistent. Furthermore, increases in attentional bias may lead to increases in craving, but this has only been demonstrated in few or ambiguous circumstances. Laboratory retraining studies have failed to show retraining effects on actual drug-taking behaviour in smokers, while in alcohol users, the findings are inconsistent. Notably across all aforementioned studies discussed in this section, non-treatment seeking individuals were recruited. In sections 1.5-1.7, I discuss the importance of examining attentional bias and AR procedures in those attempting to abstain or seeking treatment for their addiction.

### **1.5 Attentional bias and drug taking behaviour - are they related?**

In section 1.4, I discussed how the relationship between attentional bias and craving has been explored in non-treatment seeking users. In this section, I discuss the relevance of investigating attentional bias in relation to drug taking behaviour, with particular emphasis on how it might relate to lapses and relapse in those seeking treatment for their addiction.

There is a clear interest in exploring how attentional bias relates to behavioural outcomes as this could indicate how attentional bias relates to clinically relevant outcomes including

success or failure of a cessation attempt. The only ecologically valid way of investigating this is to use samples of drug users who are interested in reducing their substance-use, or are undergoing treatment. Arguably, most studies investigating this association have been small scale laboratory studies with non-treatment seeking users that have measured behavioural outcomes in an abstract way (Field et al., 2009b; Hogarth et al., 2008; Hogarth et al., 2009). For example, in the study by Field et al. (2009b) mentioned in section 1.4.2, behavioural effects of AR were assessed in current smokers by using three measures of tobacco seeking. The tasks included: a delay discounting task, in which participants were required to make hypothetical decisions about whether to accept a small number of cigarettes immediately as a reward or a larger amount after a delay; a task which measured the amount of time participants could abstain from smoking within a 30 minute timeframe; and a behavioural economic measure of how much participants were willing to pay for a cigarette after completion of retraining, ranging from low to high values. Attentional retraining had no effect on these behavioural measures of motivation to smoke; arguably these effects could be masked in samples of temporarily abstinent smokers in laboratory studies because they know that they can continue to smoke after leaving the testing session. This pattern of results may therefore be different in abstinent individuals who are motivated to reduce their substance-use.

Most relevant to the discussion here are studies that investigate attentional bias and its relation to drug treatment outcomes (Carpenter et al., 2006; Cox et al., 2002; Marissen et al., 2006; Waters et al., 2003a; Waters et al., 2003c). Patients that exhibit attentional bias may be more at risk of relapsing than those without attentional bias; for example pre-treatment bias has been shown to predict relapse in heroin addicts at three months post-

treatment, even when controlling for self-reported craving (Marissen et al., 2006). Similarly, heightened Stroop interference effects have been associated with reduced attendance at treatment and cocaine toxicology in cocaine addicts (Carpenter et al., 2006). Another study found that processing biases increased over time in alcoholic patients who relapsed during or after treatment relative to control patients and in those in whom treatment was successful (Cox et al., 2002).

In the first of the smoking cessation studies to study this relationship, 158 smokers were randomised to either a high-dose patch condition or placebo patch condition where the Stroop task was administered on the first day of quit attempts (Waters et al., 2003a). The authors found that smokers who showed greater selective processing towards smoking-related words on the first day of abstinence were significantly more likely to lapse in the short-term with daily lapse risk increasing by 30% for every 100 ms increase. Additionally, Stroop effects on the first block of trials (OR = 1.58, CI = 1.12-2.23,  $p=0.009$ ) predicted 1-week abstinence but the association was not significant between attentional bias measured in all assessments (OR = 1.50, CI = 0.98-2.29,  $p=0.06$ ).

The authors replicated the study using the visual probe task and assessed 141 smokers prior to stopping smoking (Waters et al., 2003c). As predicted, participants were significantly faster to respond to smoking-related cues than neutral cues (mean difference=2.9 ms, SD=16.8). Unlike the previous study (Waters et al., 2003a) attentional bias did not predict lapse episodes (HR=1.00, CI=0.99-1.01,  $p=0.66$ ).

A similar study investigated whether attentional bias predicted treatment success in smokers receiving standard behavioural support for smoking cessation, using both the modified visual probe task and word-Stroop task (Spiegelhalder et al., 2011). Attentional bias assessed on the visual probe task did not predict relapse as found in the study by Waters et al. (2003c). However, on the Stroop task, greater processing biases were associated with a lower risk of relapse, which is contrary to the findings in the other study by Waters et al. (2003a).

Attentional bias has been shown to predict relapse during unaided quit attempts too (Powell et al., 2010). Powell et al. (2010) found that greater processing biases on the Stroop task predicted relapse at one week but not one month or three months after quit day. Cue reactivity predicted relapse at all three times. The authors were unable to find any correlation between attentional bias and cue reactivity, which could suggest that these components tap different processes, although this remains unclear.

To summarise, only a handful of studies have explored the relationship between attentional bias and drug use in relation to relapse. In smokers attempting cessation, attentional bias has been found to predict lapses on one measure [Stroop task (Waters et al., 2003a)] but not another [visual probe task (Waters et al., 2003c)]. Furthermore, an association between attentional bias and relapse has been found in some cases, but again, this has only been found on one measure of attentional bias or through analysis of part of the data (Waters et al., 2003a). The nature of this relationship is unclear, as greater processing biases have either predicted a higher or lower risk of relapse (Spiegelhalder et

al., 2011; Waters et al., 2003a). Thus, in respect to smoking cessation the predictive validity of attentional bias is currently equivocal. Chapter 3 describes a study in which we re-examined the association between attentional bias, craving and relapse using Stroop and visual probe task measures in treatment-seeking smokers.

## **1.6 Attentional bias in abstainers and treatment-seekers**

In the current section, I discuss how some investigators have explored differences in attentional bias across subgroups of individuals and how factors like abstinence and the treatment-seeking status of substance users might relate to attentional bias.

There is some contention over whether attentional bias differs between different subgroups of smokers (e.g. never-smokers, ex-smokers and current smokers). The first study to explore this found that ex-smokers, who were enrolled in a smoking cessation programme and had been abstinent from smoking for at least one week, had an intermediate bias for smoking-related stimuli, in-between that of smokers and non-smokers (Ehrman et al., 2002). In another study, smokers who were attempting to quit and smokers without such plans had similar levels of attentional bias (Cane et al., 2009). In contrast to these studies, two studies found that ex-smokers showed a similar level of processing bias as never-smokers, while smokers exhibited more bias than both other groups (Littel & Franken, 2007; Munafo et al., 2003). In both of these studies, ex-smokers had been abstinent for at least six months rather than recently abstinent from smoking. Thus, data are conflicting but it is possible that attentional bias persists early in a quit attempt and resolves with increased duration of abstinence although no study has

examined this. However, if attentional bias persists for many months, we might speculate that if there are enduring effects of smoking cues after cessation as suggested in previous research, abstinence could be undermined in initially successful quitters.

Speculatively, it may be that substance users who are not seeking treatment or receiving treatment for substance abuse do not experience cognitions that are clinically relevant to a quit attempt. Control of attention and cognitive processes may contribute to relapse in smokers trying to quit, with both motivational and behavioural consequences. Abstaining smokers or those receiving cessation treatments may well use strategies to avoid smoking cues or suppress urges to smoke. Alcohol studies provide some tentative evidence of this in treatment-seeking alcoholics, where patients have shown attentional avoidance to alcohol-related stimuli compared to light social drinkers, i.e. faster RTs to neutral rather than alcohol-related stimuli at 500 ms stimulus presentation durations (Noel et al., 2006; Stormark et al., 1997; Townshend & Duka, 2007). However, this difference between groups is somewhat inconsistent across studies; both abstinent alcoholics and social drinkers have shown attentional avoidance in one study (Vollstadt-Klein et al., 2009), while in another, only abstinent alcoholics with low levels of craving showed attentional avoidance compared to controls (Field et al., 2013).

Altogether, the evidence suggests that factors such as abstinence or the treatment seeking status of substance users might impact on attentional bias in various ways, although the nature in which it does is unclear. While some studies demonstrate that smokers who are initially abstinent from smoking or are interested in quitting show similar levels of

attentional bias towards smoking cues than continuing smokers (Cane et al., 2009), others indicate that attentional bias might diminish over extended periods of abstinence (Littel & Franken, 2007; Munafo et al., 2003). Attentional avoidance towards drug-related stimuli has been found in treatment-seeking alcoholics (Noel et al., 2006; Stormark et al., 1997; Townshend & Duka, 2007) but it is unknown whether smokers show similar patterns of attentional processing during smoking cessation.

### **1.7 Attentional retraining in treatment-seeking populations**

In section 1.4, I described how AR has been used in laboratory studies to investigate the causal relationship between attentional bias and subjective craving. More recently, there is an increasing amount of interest in the efficacy of these procedures as a clinical tool as most standard treatments do not target attentional bias directly. This section details how AR procedures have been used to treat patients with several problems, from anxiety to addiction.

The first AR procedures were developed as an experimental paradigm in the study of anxiety-related attentional bias and later as a treatment for clinical anxiety disorders. Also known as cognitive bias modification (CBM), such procedures were designed to expose participants to a cognitive bias task encouraging them to augment or attenuate biases towards threat-related stimuli (MacLeod et al., 2002). Recent meta-analyses have revealed small to medium effects of CBM procedures on reducing attentional bias and symptoms of anxiety across clinical and non-clinical populations (Hakamata et al., 2010; Hallion & Ruscio, 2011).



A few studies have used AR as a treatment for clinically diagnosed anxiety disorders. They trained one group to avoid their selective bias and gave placebo training to the other (Amir et al., 2009a; Amir et al., 2009b; Julian et al., 2012; Schmidt et al., 2009). Using a modified visual probe task, it has been demonstrated that people with anxiety disorders have lower attention to threat-related information than patients having placebo training (Amir et al., 2009a; Amir et al., 2009b; Schmidt et al., 2009). Significant reductions in symptoms of anxiety have been found as well as remission of diagnoses in those who received AR compared to placebo training (Amir et al., 2009a), with some studies also demonstrating the maintenance of these effects up to four months post-treatment (Amir et al., 2009b; Schmidt et al., 2009).

Not all studies investigating AR found benefits for patients with anxiety disorder. In a replication of Amir et al. (2009b), Julian et al. (2012) did not find any retraining effects on attentional bias or reactivity to a stressful challenge. However, it is worth noting that this study only employed one session of training, unlike the multiple sessions delivered in the earlier studies [e.g. Amir et al. (2009a)]. A review suggested that more retraining sessions produces greater treatment effects (Hakamata et al., 2010).

In the addiction domain, only two studies to date have examined the effects of multiple AR sessions on substance users' processing biases and drug taking in people seeking to reduce or abstain (Fadardi & Cox, 2009; Schoenmakers et al., 2010). In an uncontrolled trial, Fadardi and Cox (2009) recruited hazardous and harmful drinkers interested in reducing their alcohol intake. They asked them to complete two or four weekly sessions

of AR on a modified Stroop task, respectively. After treatment was complete, processing biases towards alcohol-related stimuli reduced in both groups, as did alcohol consumption by about 10 Units/week (one Unit is equivalent to 8g of ethanol) for the harmful drinkers. These reductions were also maintained at the 3-month follow up. Uncontrolled trials in people seeking to change their behaviour are of course hard to interpret.

In the only randomised trial, Schoenmakers et al. (2010) found that alcohol-dependent patients were more able to disengage attention from alcohol-related stimuli than control patients after five sessions of AR on a modified visual probe task, given in addition to standard treatment. Moreover, relapse was delayed by over a month in patients that received AR.

Overall, AR procedures have largely shown success in reducing attentional bias and symptoms of anxiety in clinically anxious populations. These therapeutic gains have been observed following multiple sessions rather than a single session of AR. Preliminary evidence from two studies in alcohol abusers (Fadardi & Cox, 2009; Schoenmakers et al., 2010) indicates that multiple sessions of AR may lead to reductions in attentional bias for alcohol-related cues and improvements in clinically relevant outcomes, including reduced alcohol consumption and delayed relapse. At the time of writing, AR procedures had yet to be tested in smokers who were seeking to quit smoking. Chapter 3 details the first clinical trial to test multiple sessions of AR in treatment-seeking smokers.

## **1.8 Summary of introduction**

Relapse continues to be a problem in smokers who attempt to stop smoking. Although NHS SSS provide effective cessation treatments to help people stop in the short-term, there are currently no designated interventions to prevent relapse back to smoking. Most relapse prevention trials have focused on behavioural methods and pharmacotherapy to reduce the likelihood of relapse, but these have shown mixed findings. In recent times, investigators have considered the role of implicit cognitions like attentional bias in the relapse process. Using cognitive measures like the visual probe and pictorial Stroop tasks, drug users have shown greater attentional bias towards drug-related cues than neutral cues. Associations between attentional bias, craving and behavioural outcomes have been explored using cue-induced craving manipulations and attentional retraining procedures in non-treatment seeking substance users. While the data are mixed, the best evidence that attentional bias is important in addiction recovery is likely to come from experimental interventions to change it in people who are attempting to abstain from drug use. Hence, attentional retraining interventions have been developed for use in clinical populations, some of which have shown promise in improving treatment outcomes in clinically anxious patients and alcohol abusers. At the time of writing, attentional retraining had yet to be tested as a therapeutic intervention in treatment-seeking smokers; thus, we developed the first clinical trial of attentional retraining for smokers attempting to quit with NHS SSS.

## **1.9 Overview of thesis**

The goal of this thesis is to further our understanding of attentional bias and the utility of attentional retraining procedures in smokers, specifically in those attempting to quit.

The objectives of the research outlined in this thesis are therefore as follows: -

- 1) To develop, test and evaluate attentional retraining procedures for smokers;
- 2) To explore the relationship between smoking-related attentional bias, craving, withdrawal symptoms and relapse.

### ***1.9.1 Outline of chapters***

The following chapters in this thesis are set out in the chronological order that the research was carried out.

Chapter 2 describes the first empirical study in this thesis. The study was designed to pilot the length of an AR procedure suitable for use in the clinical trial described in Chapter 3. In the addiction retraining studies discussed in sections 1.4.2 and 1.7, we found no clear guidance on the optimal amount of training trials to deliver in an AR procedure, with previous studies having varied the number of trials from 512 trials (Attwood et al., 2008) to 960 trials (Field et al., 2007b) in a single session. We therefore had a sample of current smokers carry out either a short, medium or long block of attentional retraining or no training in a single session, using a modified visual probe task. Following the training

task, participants completed a cue exposure task consisting of handling a lit cigarette. We measured the effects of each block on attentional bias, subjective craving, mood and withdrawal. We further examined the number of errors made during each block length to infer attentional fatigue. Finally, we measured generalisation of retraining effects to another cognitive bias measure, the pictorial Stroop task.

Chapter 3 describes the protocol for a double-blind randomised controlled trial of attentional bias retraining in smokers attempting smoking cessation (ARTS trial, Chapter 3). This chapter describes the objectives of the study and methods used. The design of the trial focused on the delivery of multiple AR sessions to patients receiving standard behavioural support and nicotine replacement therapy for smoking cessation within NHS stop smoking clinics. Participants were randomised to either five weekly sessions of AR or placebo training (PT) on a modified visual probe task. Urge to smoke and withdrawal symptoms were measured weekly using questionnaire measures. Cognitive bias assessments were carried out on the visual probe task and the pictorial Stroop task prior to quitting, at four weeks post-quit and at the follow-up sessions at eight weeks and three months post-quit. A cue exposure task was also administered at follow-up.

Chapters 4 and 5 describe the main outcomes of the ARTS trial. As this was the first trial of AR delivered in a clinical setting to treatment-seeking smokers, Chapter 4 reports on the feasibility of running the study within NHS stop smoking clinics and the acceptability of the procedures to patients. Feasibility was assessed via response and recruitment rates at each stage of the recruitment process, in addition to attendance at clinic sessions. We

examined the acceptability of the trial procedures using a patient satisfaction questionnaire and also by looking at adherence to the training sessions.

In Chapter 5, I discuss the findings from the ARTS trial data and observational data. We examined the efficacy of the AR intervention on attentional bias, craving, withdrawal symptoms and the likelihood of relapse. We also assessed generalisation of retraining effects in two ways, firstly by looking at the effects of retraining on another cognitive bias measure, the pictorial Stroop task, and secondly by measuring attentional bias towards novel stimuli that were not used during the training task. Finally, we addressed whether attentional bias was associated with measures of dependence and smoking cessation outcomes.

Chapter 6 contains a discussion of the general conclusions from the research described in the previous chapters. Here, I also provide a summary of recommendations on future research to help advance our understanding of attentional bias and AR procedures in this field.

## **CHAPTER 2: DEVELOPMENT OF AN ATTENTIONAL RETRAINING INTERVENTION – A LABORATORY STUDY**

### **2.1 Introduction**

In section 1.3, I described how cognitive processing biases in attention towards drug-related cues have been well-documented in tobacco smokers and users of other drug substances (Lubman et al., 2000; Mogg et al., 2003). Several theoretical models of attentional bias propose that drug-related cues are able to capture the attention of a drug user, with habit-driven or motivational consequences towards drug use (Robinson & Berridge, 1993; Franken, 2003). As I mentioned in section 1.3.2.2, the visual probe task has been commonly used to measure attentional bias (MacLeod et al., 1986), in which participants are required to respond to probes that replace either drug-related stimuli or neutral stimuli. In smokers, an attentional bias towards smoking is indicated by faster reaction times to probes that appear in the location of smoking-related stimuli rather than neutral stimuli. Similarly, the addiction Stroop task has been used extensively to measure selective processing of drug-related stimuli (Cox et al., 2006b). A processing bias towards smoking is characterised by slower colour-naming of smoking-related stimuli than neutral stimuli. Both tasks have demonstrated that drug users – compared to non-drug users - show a bias towards drug-related stimuli of their choice (see sections 1.3.2.1 and 1.3.2.2).

In section 1.4, I reviewed the laboratory evidence on the association between attentional bias and craving. Using modified versions of the visual probe task, drug users have been

trained to increase or decrease attentional bias in train-to-attend and train-to-avoid experimental manipulations, while effects on craving have also been measured (Attwood et al., 2008; Field & Eastwood, 2005; Field et al., 2007b; Field et al., 2009b; McHugh et al., 2010; Schoenmakers et al., 2007). Increases in attentional bias have been associated with increases in craving (Field & Eastwood, 2005) but not consistently; some studies have found this relationship only in male participants (Attwood et al., 2008) or those aware of the experimental contingencies (Field et al., 2007b) or not at all (Field et al., 2009b; McHugh et al., 2010). While decreases in attentional bias are plausible using attentional retraining procedures, most studies have failed to find corresponding effects on craving [(Attwood et al., 2008; Field & Eastwood, 2005; Field et al., 2007b; Field et al., 2009b; McHugh et al., 2010; Schoenmakers et al., 2007) see section 1.4.2].

Differences in the experimental design of these studies may have contributed to the discrepancies found in retraining effects. As illustrated in Table 1, section 1.4.2, the amount of retraining delivered across studies has varied from 512 to 960 attentional retraining trials. It is unknown whether changes in attentional bias are dependent on the length of AR given. It may be that extending the length of AR produces stronger effects on attentional bias and craving, where a linear dose-response relationship would be observed. However, an alternative possibility is that a longer AR session may have detrimental effects on attentional bias and craving because the risk of participants' experiencing boredom and fatigue is increased. In this instance, we might find a curvilinear relationship with training, due to fatigue effects involved with doing a repetitive task.



The purpose of the present study was to test the acceptability an AR intervention for use in a forthcoming smoking cessation trial. The ARTS trial, (a double blind randomised controlled trial of attentional bias retraining in smokers attempting smoking cessation) will use the modified visual probe task described above as a treatment tool. For these procedures to have any clinical value in the treatment of smokers who are seeking to quit, it is necessary to establish how much training is needed in order to detect any effects on attentional bias and craving. Furthermore, it is important to develop an intervention of a length that is both tolerable for patients and practical for practitioners to deliver alongside usual care in a NHS stop smoking clinic.

We therefore aimed to investigate the extent to which the length of AR mediates attentional bias and subjective craving in tobacco smokers. We also sought to explore the relationship between AR and fatigue, which was inferred from the number of errors made during training. We used a between-subjects design to compare participants in an AR group who were trained away from smoking-related stimuli with a control group who received no training towards any particular stimulus-type. Unlike in the previous studies (Attwood et al., 2008; Field et al., 2009b), we did not include a group that was trained towards smoking-related stimuli because our primary interest lies in the potential clinical translation of AR procedures.

Participants were further randomised to receive a short, medium or long block of AR or no training, in order to examine the effects of varying the length of the procedure. We included a cue-exposure task to measure cue-reactivity immediately after the procedure,

which has consistently been shown to evoke cue-induced craving (Attwood et al., 2008; Carter & Tiffany, 2001; Sayette et al., 2001). Finally, we examined whether any effects of AR could generalize to other measures of attentional bias, namely on a pictorial Stroop task. The issue of generalization of retraining effects in tobacco smokers has only been explored in one of the earlier studies (Field et al., 2009b), but the effects of training did not generalise to performance on a different task.

## **2.2 Methods**

### **2.2.1 *Participants***

Seventy-two non-treatment seeking smokers (36 males and 36 females) were recruited from the general population via posters and online advertising. Inclusion criteria included a minimum age of 18 years and self-reported tobacco smoking of at least five cigarettes per day. Participants were also required to have normal or corrected-to-normal vision. Participants were excluded if they had a severe acute or chronic medical or psychiatric illness, or if they were using illicit substances (excluding cannabis).

The study was approved by the Faculty of Science Research Ethics Committee at the University of Bristol and the Life and Health Sciences Ethical Review Committee at the University of Birmingham.

### **2.2.2 Materials**

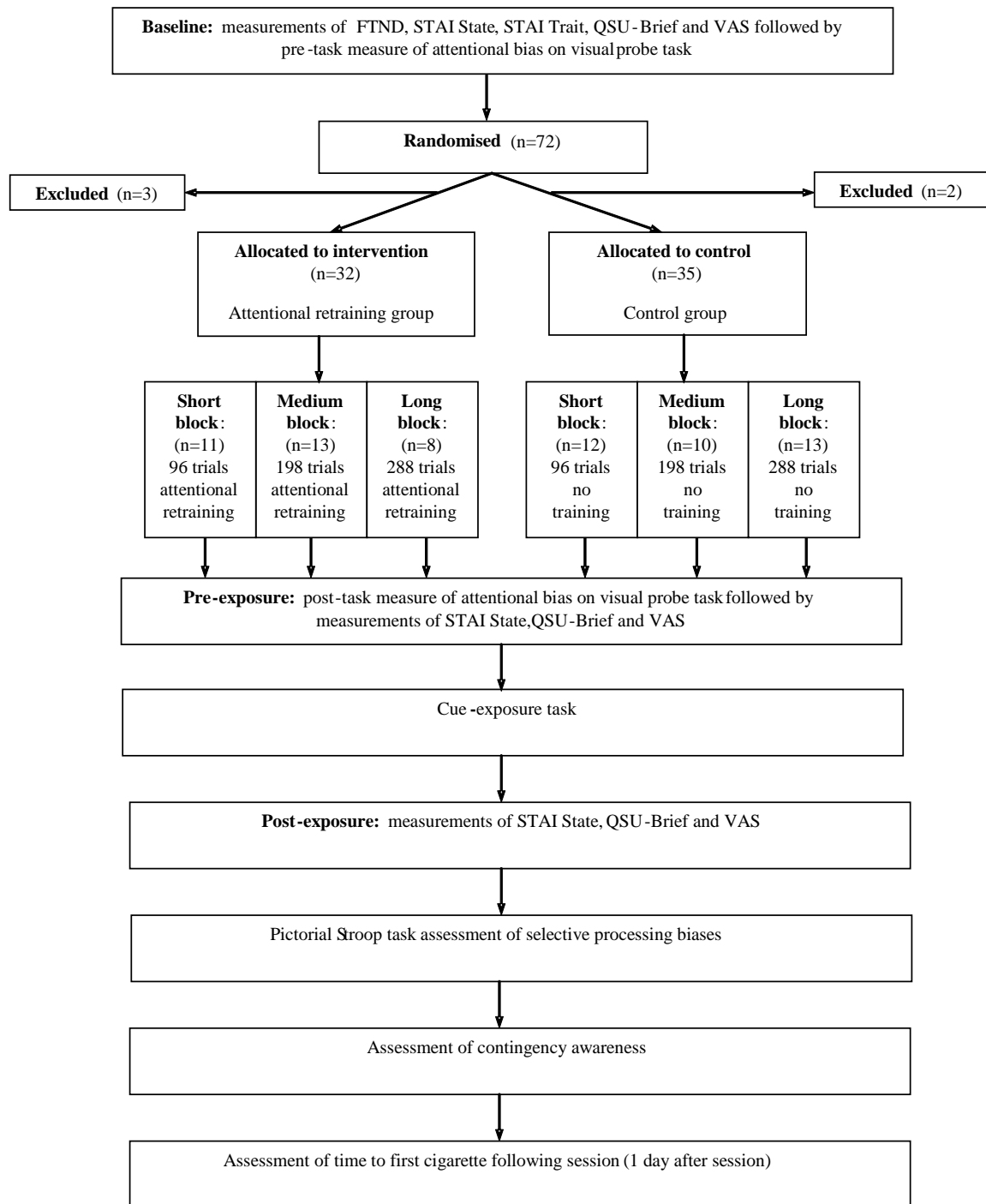
Twelve pairs of smoking-related and matched neutral pictures were used, as tested and applied in previous research (Attwood et al., 2008; Bradley et al., 2008; Mogg et al., 2003). Each set of pictures consisted of a colour photograph of a smoking-related stimulus or scene (e.g. a close-up of a pack of cigarettes) matched as closely as possible to another photograph containing no smoking-related content. An additional four neutral picture pairs were used in practice trials.

The same questionnaire measures were used as in the Attwood et al. (2008) study. This comprised of the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1991), a six-item measure assessing severity of nicotine dependence; the Spielberger State-Trait Anxiety Inventory state and trait sub-scales (STAI-State and STAI-Trait) (Spielberger et al., 1983), each containing 20 items rated on a four-point scale ranging from “not at all” to “very much so” on the STAI-State and “almost never” to “almost often” on the STAI-Trait; the Questionnaire of Smoking Urges - Brief (QSU-Brief) (Cox et al., 2001), a nine-item measure of urge to smoke rated on a seven-point scale ranging from “strongly disagree” to “strongly agree”; and visual analogue scales (VAS) for items including “happy”, “drowsy”, “depressed”, “anxious”, “energetic”, “irritable”, and “craving a cigarette” rated on a 100 mm (millimetre) scale from “not at all” to “extremely”.

### **2.2.3 Procedure**

Figure 3 provides a schematic overview of the allocation of participants and procedures. Participants were tested between the hours of 09:00 and 12:00. Participants were asked to abstain from cigarette smoking for 12 hours prior to the study, as stated in the participant information sheet (Appendix 1). Participants provided informed consent (Appendix 2) and samples of expired carbon monoxide on a MicroCO Meter (Care Fusion Ltd) to confirm temporary abstinence from smoking upon arrival. They then completed a questionnaire battery where baseline measurements (FTND, STAI-State, STAI-Trait, QSU-Brief and VAS) were taken immediately prior to the visual probe task (Appendix 3).

The visual probe task consisted of blocks of practice trials, test trials and attentional retraining trials. The structure of each trial was similar across trials. Each trial began with a fixation cross displayed in the centre of the computer screen for 500 ms. A picture pair of smoking-related and neutral pictures was then presented for 500 ms. This picture pair disappeared and a visual probe, either a circle or a square, was presented in the location formerly occupied by one of the pictures. Participants were required to discriminate the identity of the probe and respond accordingly by pressing the up or down arrow keys on the keyboard as quickly as possible. The probe remained on the screen until a response was detected by the program, after which there was a 500 ms interval before the next trial began. On each trial, participants' response latencies and accuracy were recorded. Each block of trials was presented in a new random order for each participant, using EPrime version 2 (Psychology Software Tools Inc., Pittsburgh PA).



**Figure 3. Schematic overview of participant flow and procedures**

Participants first completed eight practice trials in which neutral picture pairs were presented in order to familiarize themselves with the task. This was followed by one block of test trials, which provided a pre-task measure of attentional bias. The test comprised a total of 96 trials, across which the visual probes appeared in the location of the smoking-related and neutral pictures with equal frequency. Following the test trials, participants were randomized to complete either a modified version of the visual probe task designed to train attention away from smoking-related stimuli (attentional retraining group) or no training towards any stimulus-type (control group). Within each group, participants were randomly allocated to receive one block, two blocks or three blocks of attentional retraining or no training, comprising a total of 96, 192 and 288 trials, respectively. For participants in the AR group, the visual probes always appeared in the location of the neutral pictures in every block. For participants in the control group, the visual probes were presented in the location of the smoking-related and neutral pictures with equal frequency. After AR or no training, participants completed another block of 96 test trials, which provided a post-task measure of attentional bias.

Participants then provided pre-exposure mood and urge to smoke ratings (STAI-State; QSU-Brief; VAS). Subsequently, participants took part in a cue-exposure task. Standardized instructions for the task were delivered via a digital recorder. During the 3-minute exposure, participants were seated in front of their own brand of cigarette, a lighter and an ashtray. They were instructed to pick up the cigarette, light it but not smoke it, and imagine what it would be like to smoke the cigarette before extinguishing it in the ashtray. Following the task, post-exposure mood and urge to smoke ratings were taken (STAI-State; QSU-Brief; VAS).

After the cue exposure task, participants completed a pictorial Stroop task. The same 12 picture pairs of smoking-related and matched neutral pictures that were used in the visual probe task were used during this task. Each picture, which had either an outline of a red, blue, yellow or green border, was presented centrally on the computer screen. Participants were required to indicate the colour of the border, while ignoring the picture, by pressing one of four corresponding colour-labelled keys on the keyboard, as quickly as possible. Participants received eight practice trials in which neutral pictures were presented first, followed by 96 trials, presented in two blocks of 48 trials.

At the end of the session, participants were asked a question about their awareness of the experimental contingencies during the visual probe task. Participants were asked whether they thought that the visual probes always appeared in the location of the smoking-related pictures, the neutral pictures or both with equal frequency. They were then debriefed and reimbursed £10 for their time (Appendix 4). On the next day, all participants were contacted for follow-up and asked when they had their first cigarette after leaving the session. If this was within 30 minutes of leaving the session, participants were asked to specify the number of minutes at 5-minute intervals (e.g. “within 10-15 minutes”).

## **2.2.4 Data analysis**

### *2.2.4.1 Primary analyses*

Attentional bias scores on the visual probe task were calculated in the following way. A reaction time (RT) was produced for each correct response made on each trial where the

probe replaced either the smoking-related picture or neutral picture. A mean RT was calculated for all RTs produced for smoking-related pictures and all RTs produced for neutral pictures. A score for attentional bias was calculated by subtracting the overall mean RT to smoking-related pictures from the mean RT to neutral pictures, where a positive score indicated a bias towards smoking cues and a negative score indicated a bias towards neutral cues. These scores were used to examine retraining effects on attentional bias firstly by group and secondly by block length, in a series of analyses of covariance (ANCOVAs). Mixed model analyses of variance (ANOVAs) were also performed using mean RTs for each picture type. Where significant interactions were found, further analyses were performed using ANOVAs and t-tests (details provided within each subsection below). For all mixed model ANOVAs, Greenhouse-Geisser was used to report all F-values. T-tests were two-tailed and an alpha level of 0.05 was set. These analyses were performed using PASW Statistics 18 (SPSS, Inc., 2009, Chicago, IL, USA).

In order to investigate retraining effects on subjective craving by group and block length over time, data were analysed using mixed effects regression models with an autoregressive variance-covariance structure. The reasons for choosing this approach over univariate methods were three-fold; firstly, mixed effects regression takes into account that the rate of change in craving across time varies between participants and so estimates are produced for each participant, while ANOVA relies on averaging across all participants and thus fails to capture this variation (Hedeker, 2004). Secondly, an autoregressive modelling structure takes into consideration that repeated craving measurements taken closer together in time on the same participant are likely to be more highly correlated than measurements that are taken further apart in time; ANOVA on the



other hand, assumes that all assessments are similarly correlated over time (Vittinghoff et al., 2004). Finally, due to the complexity of the experimental design, mixed effects regression modelling was the most practical way for me to examine the three-way interaction between group, block length and time. This modelling technique was used on the QSU-Brief scores and the single VAS item “craving a cigarette”. Regression coefficients, p-values and 95% confidence intervals (CI) were derived from the models. These analyses were implemented in Stata 11.0 (StataCorp, 2009, College Station, TX: StataCorp LP).

#### 2.2.4.2 *Secondary analyses*

We investigated the effects of AR on mood and withdrawal over time using scores from the STAI-State and VAS measures in mixed model ANOVAs. To control for multiple testing and avoid the risk of making a Type 1 error, an alpha level of 0.008 was set for the VAS measures following a Bonferroni adjustment for six independent tests.

To examine whether AR affected selective processing biases on the pictorial Stroop task, mean RTs to colour-naming trials of neutral pictures were subtracted from the mean RTs to colour-naming trials of smoking-related pictures to give an overall Stroop bias score. Slower RTs to smoking-related pictures indicated a processing bias towards smoking cues, while faster RTs to neutral pictures indicated a bias towards neutral cues. T-tests were used to compare Stroop bias scores between groups and at each block length. Mean RTs for each picture type were also examined in mixed model ANOVAs.

Contingency awareness was assessed using a chi-squared test and time to first cigarette questionnaire data were analysed using Mann-Whitney U.

Error data from training trials were analysed using multilevel logistic regression to examine the effects of each block length on the number of errors made. Errors consisted of incorrect responses to the probe, including responses of <200 ms that were considered too quick to represent true attentional processing and responses of >1500 ms, which were considered too slow (including those that timed out, i.e. no response was made). Odds ratios (OR) and 95% confidence intervals (CI) were compared. Finally, linear regression was used to examine error frequency on attentional bias scores, with error treated as a categorical variable (0-4 errors/5+ errors).

## **2.3 Results**

### **2.3.1 *Data reduction***

Test trials comprising of errors were removed from visual probe task data; error rates were 7.4% pre-training and 4.3% post-training. All visual probe task data were missing from three participants and post-training data were missing for one participant due to a computer error. All visual probe task data were excluded for one participant based on a high percentage of trial errors (51%) and outlying RTs (mean <200 ms).

Trials with errors were also removed from pictorial Stroop task data; the error rate was 3.8%. All pictorial Stroop task data were excluded for one participant due to a high percentage of trial errors (62.5%). Results are reported for  $n=67$  participants.

### 2.3.2 Participant characteristics

The sample included 33 males and 34 females, aged between 18 and 49 ( $M=23.91$ ,  $SD=6.22$ ). Participants smoked between 5 and 27 cigarettes per day ( $M=9.97$ ,  $SD=4.81$ ) and started smoking between the ages of 13 and 24 ( $M=16.36$ ,  $SD=2.40$ ). Participants had an FTND score between 0 and 7 ( $M=2.60$ ,  $SD=2.04$ ). Table 2 shows summary data for baseline measures by group allocation and Table 3, Table 4 and Table 5 by length of block allocation.

**Table 2. Baseline characteristics of participants by group**

	All ( $n= 67$ )	Attentional retraining ( $n= 32$ )	Control ( $n=35$ )
	M (SD)	M (SD)	M (SD)
Gender ratio (M:F)	33:34	17:15	16:19
Age (years)	23.91 (6.22)	24.03 (6.07)	23.80 (6.44)
Cigarettes smoked per day	9.97 (4.81)	10.16 (5.27)	9.80 (4.41)
Age started smoking (years)	16.36 (2.40)	16.91 (2.61)	15.86 (2.10)
FTND*	2.60 (2.04)	2.50 (2.14)	2.69 (1.97)
STAI-Trait	41.60 (9.94)	42.00 (10.40)	41.23 (9.64)
STAI-State at baseline	37.25 (8.96)	35.97 (7.03)	38.42 (10.38)
QSU-Brief total at baseline	33.12 (12.40)	29.34 (10.74)	36.57 (12.95)
VAS craving at baseline	42.99 (19.63)	40.06 (19.36)	45.66 (19.77)

\*Fagerstrom Test for Nicotine Dependence, scored from 0-10

**Table 3. Baseline characteristics of participants by allocation to short block length**

Short block length	All (n= 23)	Attentional retraining (n= 11)	Control (n=12)
	M (SD)	M (SD)	M (SD)
Gender ratio (M:F)	15:8	8:3	7:5
Age (years)	24.13 (6.15)	25.27 (7.24)	23.08 (5.04)
Cigarettes smoked per day	10.78 (5.19)	10.82 (6.34)	10.75 (4.16)
Age started smoking (years)	16.65 (2.27)	16.91 (2.81)	16.42 (1.73)
FTND*	2.65 (2.19)	2.55 (2.42)	2.75 (2.05)
STAI-Trait	38.26 (9.13)	36.55 (8.92)	39.83 (9.42)
STAI-State at baseline	33.05 (8.43)	31.00 (4.86)	35.09 (10.79)
QSU-Brief total at baseline	29.00 (11.80)	27.45 (10.62)	30.36 (13.74)
VAS craving at baseline	37.39 (20.46)	35.64 (19.27)	38.00 (23.01)

\*Fagerstrom Test for Nicotine Dependence, scored from 0-10

**Table 4. Baseline characteristics of participants by allocation to medium block length**

Medium block length	All (n= 23)	Attentional retraining (n= 13)	Control (n=10)
	M (SD)	M (SD)	M (SD)
Gender ratio (M:F)	10:13	5:8	5:5
Age (years)	25.57 (7.56)	23.69 (5.82)	28.00 (9.10)
Cigarettes smoked per day	9.35 (5.30)	9.15 (5.08)	9.60 (5.84)
Age started smoking (years)	16.83 (2.33)	17.15 (1.95)	16.40 (2.80)
FTND*	2.48 (2.13)	2.23 (2.24)	2.80 (2.04)
STAI-Trait	43.61 (11.02)	43.85 (11.97)	43.30 (10.26)
STAI-State at baseline	40.70 (9.65)	39.55 (8.07)	42.11 (11.66)
QSU-Brief total at baseline	33.30 (13.79)	31.18 (11.09)	36.67 (15.08)
VAS craving at baseline	43.57 (21.71)	44.45 (18.26)	43.56 (24.25)

\*Fagerstrom Test for Nicotine Dependence, scored from 0-10

**Table 5. Baseline characteristics of participants by allocation to long block length**

Long block length	All (n= 21)	Attentional retraining (n= 8)	Control (n=13)
	M (SD)	M (SD)	M (SD)
Gender ratio (M:F)	8:13	4:4	4:9
Age (years)	21.86 (3.97)	22.88 (5.11)	21.23 (3.14)
Cigarettes smoked per day	9.76 (3.82)	10.88 (4.29)	9.08 (3.50)
Age started smoking (years)	15.52 (2.50)	16.50 (3.46)	14.92 (1.55)
FTND*	2.67 (1.85)	2.88 (1.73)	2.54 (1.98)
STAI-Trait	43.05 (9.01)	46.40 (6.59)	40.92 (9.86)
STAI-State at baseline	38.38 (7.28)	37.88 (3.83)	38.69 (8.91)
QSU-Brief total at baseline	37.43 (10.31)	31.75 (9.87)	40.92 (9.25)
VAS craving at baseline	48.48 (15.00)	43.63 (19.24)	51.46 (11.57)

\*Fagerstrom Test for Nicotine Dependence, scored from 0-10

### 2.3.3 *Attentional bias at baseline*

A one-sample t-test against zero indicated that there was no significant attentional bias towards smoking cues in the sample at baseline ( $t[66]=0.46$ ,  $p=0.65$ ). Although the AR group exhibited a higher attentional bias (mean difference=2.42), this was not statistically significant ( $t[65]=0.22$ ,  $p=0.83$ ). As can be seen in Table 6, mean RTs for smoking-related pictures across both groups were lower than mean RTs for neutral pictures at baseline, suggesting that participants were responding faster in the predicted direction (for mean RTs by block length, see Appendix 5).

**Table 6. Pre-training and post-training attentional bias scores by group**

	Attentional retraining (n=32)	Control (n=35)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	660.50 (124.64)	676.56 (128.25)	-16.06	-0.52	0.61	(-77.87, 45.75)
RT for neutral stimuli	664.27 (129.20)	677.90 (129.41)	-13.63	-0.43	0.67	(-76.80, 49.53)
Attentional bias	3.77 (51.39)	1.34 (38.39)	2.42	0.22	0.83	(-19.59, 24.43)
Post-training						
RT for smoking stimuli	611.56 (127.69)	603.93 (102.82)	7.63	0.27	0.79	(-48.71, 63.98)
RT for neutral stimuli	619.59 (130.62)	611.21 (117.41)	8.38	0.28	0.78	(-52.14, 68.90)
Attentional bias	8.03 (32.31)	7.29 (45.62)	0.75	0.08	0.94	(-18.71, 20.20)
Change score attentional bias	4.27 (64.02)	5.94 (52.95)	-1.68	-0.12	0.91	(-30.25, 26.89)

*RT - reaction time (milliseconds)*

#### **2.3.4 Association between attentional bias and subjective craving at baseline**

To examine whether the visual probe task measure of attentional bias was correlated with subjective craving measures at baseline, Pearson's correlations were performed between the baseline attentional bias scores, QSU-Brief scores and VAS score for the item "craving a cigarette" on all participants. A strong positive correlation was found between both craving measures ( $r=+0.87$ ,  $p<0.001$ ), but neither measure was correlated with the attentional bias scores ( $p>0.52$ ,  $r_s<-0.05$ ).

#### **2.3.5 Effects of attentional retraining on attentional bias**

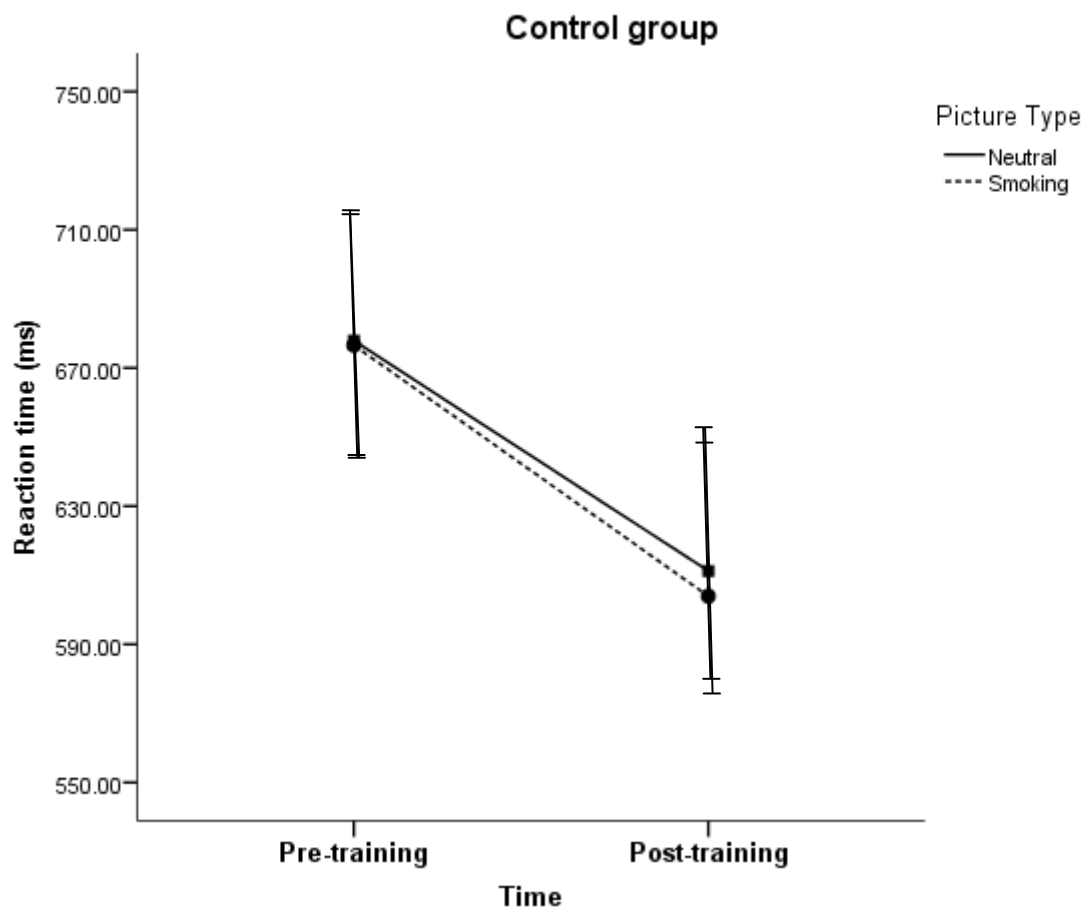
A one-way between-groups analysis of covariance (ANCOVA) was performed using pre-training attentional bias scores as the covariate.

After adjusting for pre-training attentional bias scores, no significant differences were found between groups in post-training attentional bias scores ( $F[2,64]=0.004$ ,  $p=0.95$ ). Similarly, in a  $2 \times 2$  between-groups ANCOVA with participant gender as an additional factor, there were no significant main effects or interactions ( $F_s < 0.27$ ,  $p_s > 0.61$ ).

The analyses were re-run in a  $3 \times 2$  ANCOVA with the inclusion of block length (short, medium, long) but no significant main effects or interactions were found ( $F_s < 2.39$ ,  $p_s > 0.10$ ).

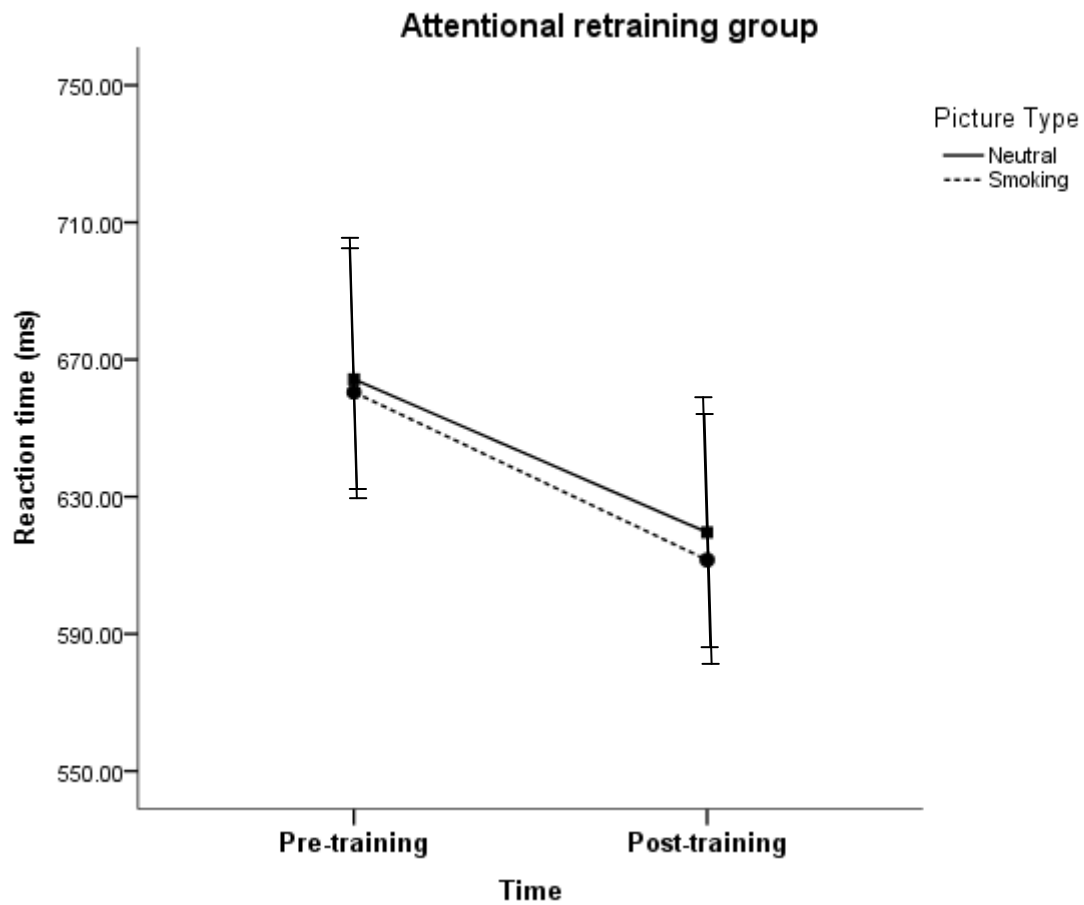
To examine whether there were group differences between pre and post training RT scores to each picture type, data were analysed using a  $2 \times 2 \times 2$  mixed model ANOVA with group (attentional retraining/control) as the between-subjects factor and picture type (smoking-related pictures/neutral pictures) and time (pre-training/post-training) as the within-subjects factors. There was a significant effect of time ( $F[1,65]=22.22$ ,  $p < 0.001$ , partial  $\eta^2=0.26$ ) but there were no other significant main effects or interactions ( $F_s < 1.83$ ,  $p_s > 0.18$ ). Within-subjects t-tests, performed separately on each group, indicated that participants in the AR group responded significantly faster to both smoking-related pictures ( $t[31]=2.17$ ,  $p < 0.04$ ) and neutral pictures ( $t[31]=2.61$ ,  $p < 0.01$ ) post-training, as did the control group for smoking-related pictures ( $t[34]=4.18$ ,  $p < 0.001$ ) and neutral pictures ( $t[34]=4.26$ ,  $p < 0.001$ ) post-training, which may reflect practice effects (Figure 4).

a)





b)



**Figure 4. Pre-training and post-training mean reaction time scores (in milliseconds) to neutral and smoking-related pictures. Data are shown separately for a) control group (n=35) and b) attentional retraining group (n=32)**

When block length (short, medium, long) was added as an additional between-subjects factor in the mixed model ANOVA described above, there was a significant main effect of time ( $F[1,61]23.21$ ,  $p<0.001$ , partial  $\eta^2=0.28$ ) and a 3-way interaction of group x block length x picture type ( $F[2,61]3.41$ ,  $p<0.04$ , partial  $\eta^2=0.10$ ). There was also a significant block length x time interaction ( $F[2,61]3.63$ ,  $p<0.03$ , partial  $\eta^2=0.11$ ). No other significant main effects or interactions were observed ( $F_s<3.10$ ,  $p_s>0.09$ ).

We investigated the source of this interaction by conducting a 2 x 2 x 2 mixed model ANOVA by block length. There was a significant group x picture type interaction effect at the medium block length ( $F[1, 21]6.70$ ,  $p<0.02$ , partial  $\eta^2=0.24$ ) and main effects of time at the medium block length ( $F[1, 21]13.13$ ,  $p<0.002$ , partial  $\eta^2=0.39$ ) and long block length ( $F[1, 21]19.26$ ,  $p<0.001$ , partial  $\eta^2=0.50$ ). No significant main effects or interactions were found at the short block length ( $ps>0.25$ ).

Within subjects t-tests revealed that participants in the AR group who were allocated to the medium block length responded significantly faster to both smoking-related pictures ( $t[12]=4.92$ ,  $p<0.001$ ) and neutral pictures ( $t[12]=5.18$ ,  $p<0.001$ ) post-training. While the AR group responded faster to both picture types overall, participants were quicker to respond to neutral pictures than smoking-related pictures (mean difference=-6.33 ms). In contrast, the control group were quicker to respond to smoking-related pictures than neutral pictures (mean difference=18.43 ms).

### ***2.3.6 Effects of attentional retraining on subjective craving***

#### *2.3.6.1 Statistical modelling of QSU-Brief and VAS scores*

Two independent, fully specified, mixed-effects regression models of subjective craving with QSU-Brief scores and VAS “craving a cigarette” scores as outcome variables against the explanatory variables, group (attentional retraining/control), time (baseline/pre-exposure/post-exposure) and block length (short/medium/long) were constructed. In all models, the reference categories were the control group, time at baseline and the short

block length. Participant ID was treated as the random effects part of the models. Participant gender was entered in the model as a covariate since this was found to be a moderator of retraining effects on craving in a previous study (Attwood et al., 2008).

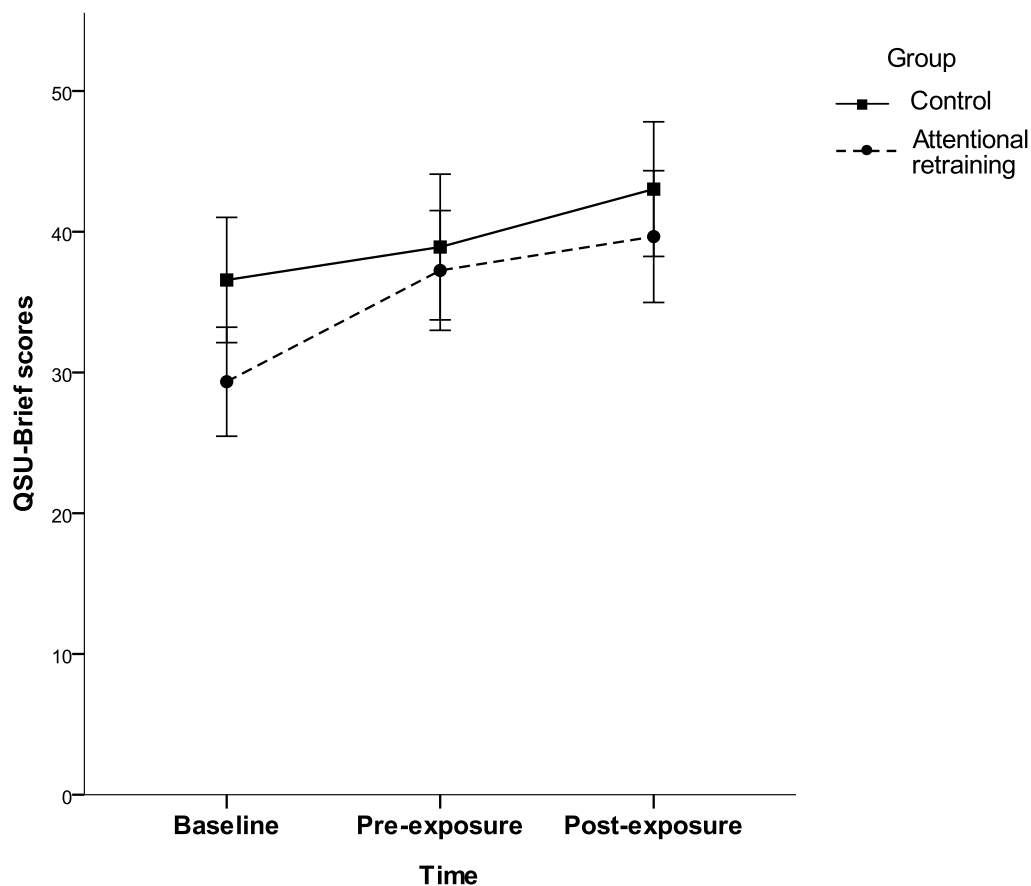
The fully specified models included all main effects, lower order two-way interactions and a three-way interaction between group, time and block length. Stepwise regression was carried out using backward elimination to remove sets of interactions that failed to reach the significance threshold ( $p < 0.05$ ) and thus had little influence on the outcome variable. Additionally, model comparisons were performed using chi squared to assess goodness of fit and qualify the removal of any interactions. The overall aim was to produce the most parsimonious model of QSU-Brief scores and VAS scores to best explain the data.

The fully specified models were used to produce linear combinations of the coefficients in order to estimate the overall effect of AR on QSU-Brief scores and VAS craving scores between groups at each time point and block length.

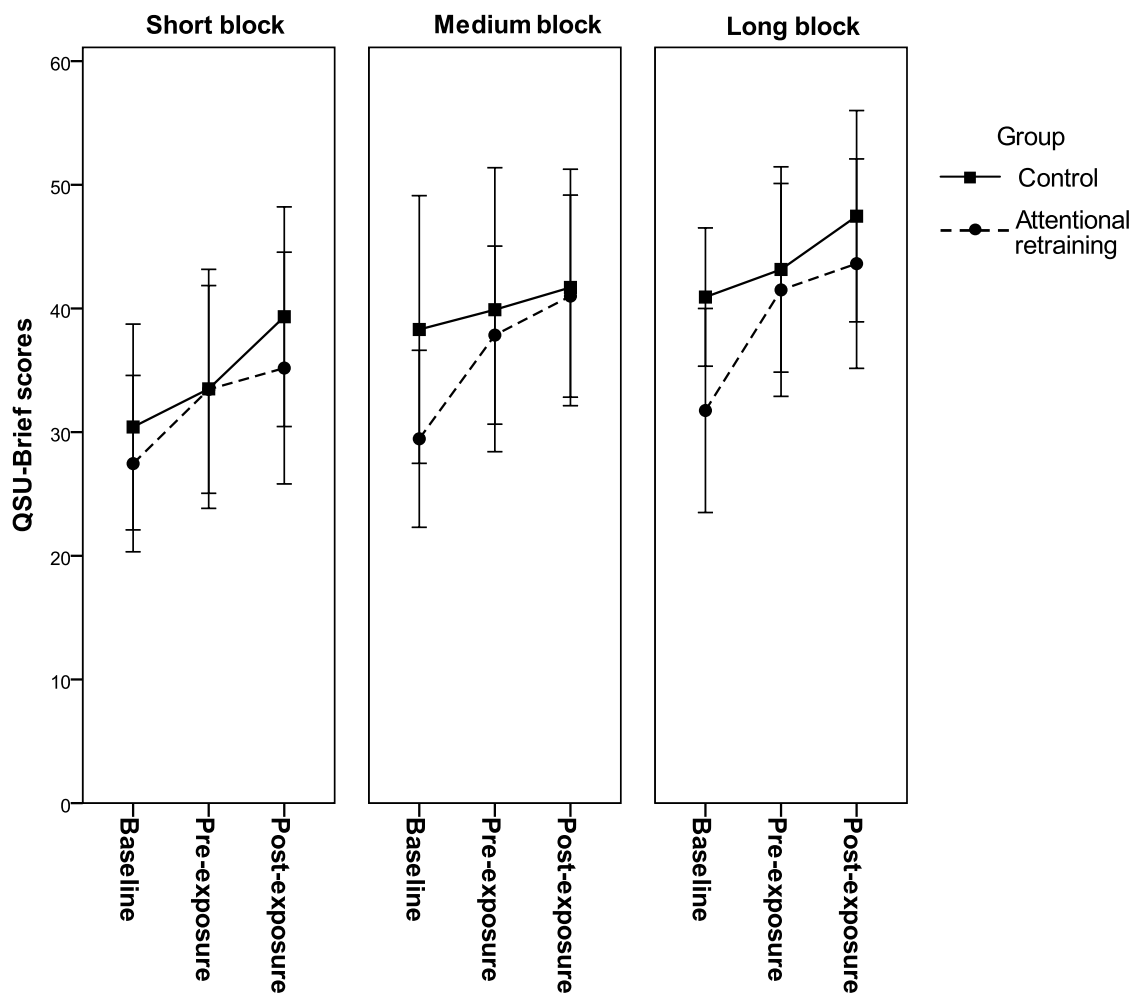
At each step of modelling, diagnostic checks were carried out on the residuals of each model using scatter plots to check normality (see Appendix 6). Box and whisker plots were constructed to check the distribution of scores (see Appendix 7).

### 2.3.6.1.1 QSU-Brief

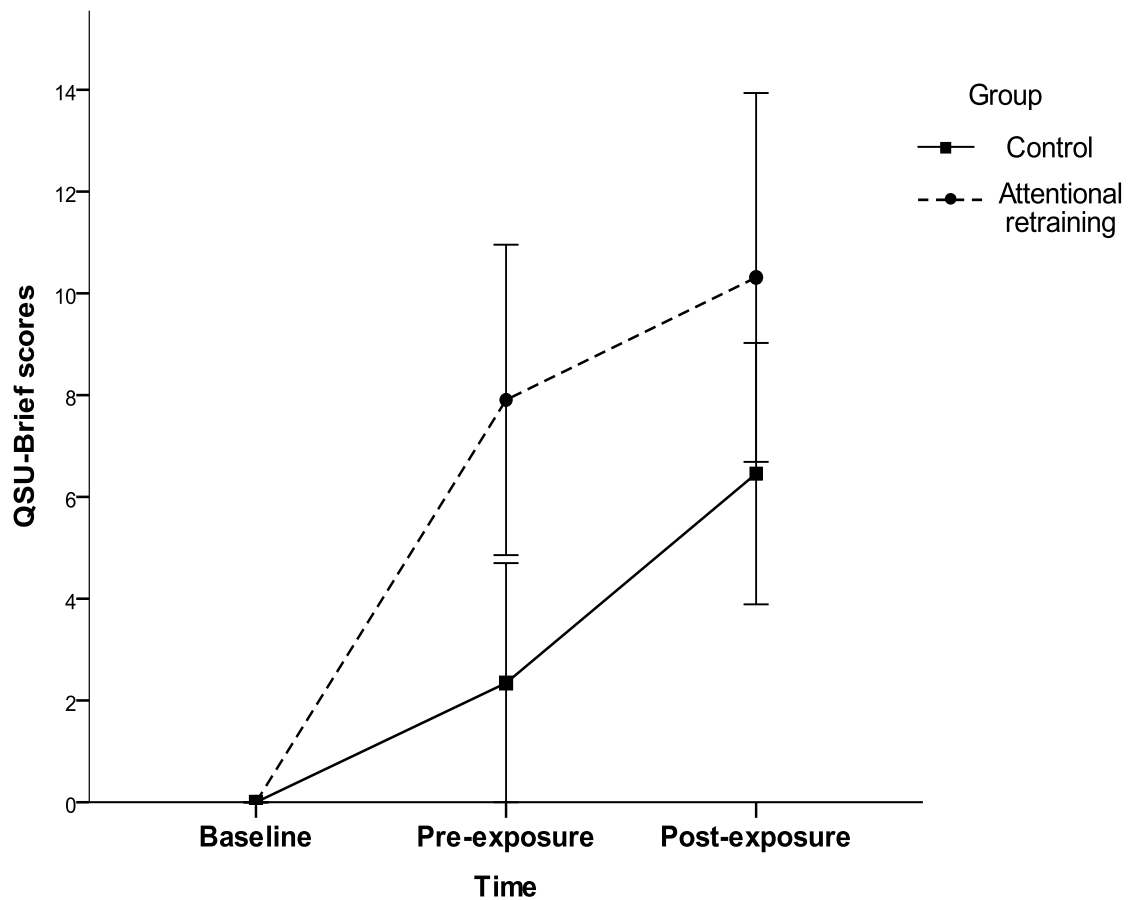
Figure 5 and Figure 6 illustrate the mean scores for the QSU-Brief by group and block length, respectively. In both groups and at each block length, there was a general increase in craving over time. The change in craving was greater in the AR group compared to the control group from baseline to pre-exposure (mean difference=5.56) but not from pre-exposure to post-exposure, where the difference was smaller in the AR group compared to the control group (mean difference=-1.71, see Figure 7). A similar pattern was observed across each block length apart from the medium block length, where the change in craving from pre-exposure to post-exposure was marginally greater in the AR group compared to the control group (mean difference=1.35, see Appendix 8 for details).



**Figure 5. Mean (95% CI) QSU-Brief craving scores at baseline, pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35)**



**Figure 6.** Mean (95% CI) QSU-Brief craving scores at baseline, pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35) by short, medium and long block length



**Figure 7. Mean (95% CI) change in QSU-Brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35)**

The most parsimonious mixed-effects model of QSU-Brief scores was reached through elimination of non-significant interactions between group, time and block length, time by block length and group by block length (Table 7). The inclusion of participant gender did not significantly improve the fit of the model nor alter the coefficients substantially; therefore this was discarded during initial modelling steps. Model comparisons indicate that the parsimonious model was similar to the fully specified model because there was no

significant difference in fit; while there were fewer degrees of freedom in the parsimonious model, there was no significant loss in the log-likelihood (Table 8).

**Table 7. Mixed-effects models of QSU-Brief scores over time by group and block length**

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects										
Group <sub>1</sub>	-3.13	0.54	-2.96	0.56	-5.58	0.25	-5.50	0.26	-6.80	0.03
Gender <sub>2</sub>	-1.20	0.68								
Time (pre-exposure) <sub>3</sub>	3.08	0.12	3.08	0.12	1.78	0.28	2.34	0.05	2.34	0.05
Time (post-exposure) <sub>3</sub>	8.92	0.001	8.92	0.001	6.43	0.003	6.46	0.001	6.46	0.001
Block length (medium) <sub>4</sub>	7.98	1.53	7.88	0.13	5.53	0.27	5.29	0.28	4.66	0.17
Block length (long) <sub>4</sub>	10.84	2.19	10.51	0.03	8.94	0.06	9.36	0.04	8.18	0.02
Intercept	30.92		30.42		31.67		31.58		32.2	
Interactions										
Group x Time (pre-exposure)	2.92	0.31	2.92	0.31	5.64	0.001	5.56	0.001	5.56	0.001
Group x Time (post-exposure)	-1.19	0.75	-1.19	0.75	4.01	0.07	3.86	0.08	3.86	0.08
Group x Block length (medium)	-5.57	0.44	-5.88	0.42	-1.31	0.85	-1.31	0.85		
Group x Block length (long)	-6.27	0.40	-6.21	0.41	-2.78	0.69	-2.78	0.69		
Time (pre-exposure) x Block length (medium)	-1.48	0.61	-1.48	0.61	0.47	0.82				
Time (pre-exposure) x Block length (long)	-0.85	0.76	-0.85	0.76	1.17	0.58				
Time (post-exposure) x Block length (medium)	-5.52	0.14	-5.52	0.14	-0.70	0.79				
Time (post-exposure) x Block length (long)	-2.38	0.50	-2.38	0.50	0.61	0.82				
Group x Time (pre-exposure) x Block length (medium)	3.87	0.34	3.87	0.34						
Group x Time (pre-exposure) x Block length (long)	4.60	0.27	4.60	0.27						
Group x Time (post-exposure) x Block length (medium)	9.33	0.07	9.33	0.07						
Group x Time (post-exposure) x Block length (long)	6.53	0.23	6.53	0.23						



Table 7 continued

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Random effects										
Participant ID, intercept (SD)	8.89		8.91		8.22		8.23		8.28	
-2*log likelihood	-704.56		-704.64		-706.5		-706.8		-706.88	

*Model 1: craving score by group, gender, time, block length and interaction terms group x time x block length, group x time, group x block length, time x block length*

*Model 2: craving score by group, time, block length and interaction terms group x time x block length, group x time, group x block length, time x block length*

*Model 3: craving score by group, time, block length and interaction terms group x time, group x block length, time x block length*

*Model 4: craving score by group, time, block length and interaction terms group x time, group x block length*

*Model 5: craving score by group, time, block length and interaction term group x time*

*<sub>1</sub> Reference category is control group, <sub>2</sub>Reference category is males, <sub>3</sub>Reference category is time (baseline), <sub>4</sub>Reference category is block length (short)*

**Table 8. Difference in fit between models of QSU-Brief scores over time**

	LL <sub>1</sub>	LL <sub>2</sub>	Chi squared	df	p
Model 1 to 2	-704.56	-704.64	0.08	1	0.78
Model 2 to 3	-704.64	-706.50	1.86	4	0.76
Model 2 to 4	-704.64	-706.80	2.16	8	0.98
Model 2 to 5	-704.64	-706.88	2.24	10	0.99

*Model 1: craving score by group, gender, time, block length and interaction terms group x time x block length, group x time, group x block length, time x block length*

*Model 2: craving score by group, time, block length and interaction terms group x time x block length, group x time, group x block length, time x block length*

*Model 3: craving score by group, time, block length and interaction terms group x time, group x block length, time x block length*

*Model 4: craving score by group, time, block length and interaction terms group x time, group x block length*

*Model 5: craving score by group, time, block length and interaction term group x time*

*LL<sub>1</sub> - loglikelihood of hierarchically superior model; LL<sub>2</sub> - loglikelihood of comparison model*

The only significant interaction found in the parsimonious model was a group by time (pre-exposure) interaction ( $\beta=5.56$ ,  $p<0.001$ ). The absence of any significant interactions by block length suggests that effects of group or time on craving were not mediated by block length; as can be seen in Figure 6, there was no difference in trend across blocks.

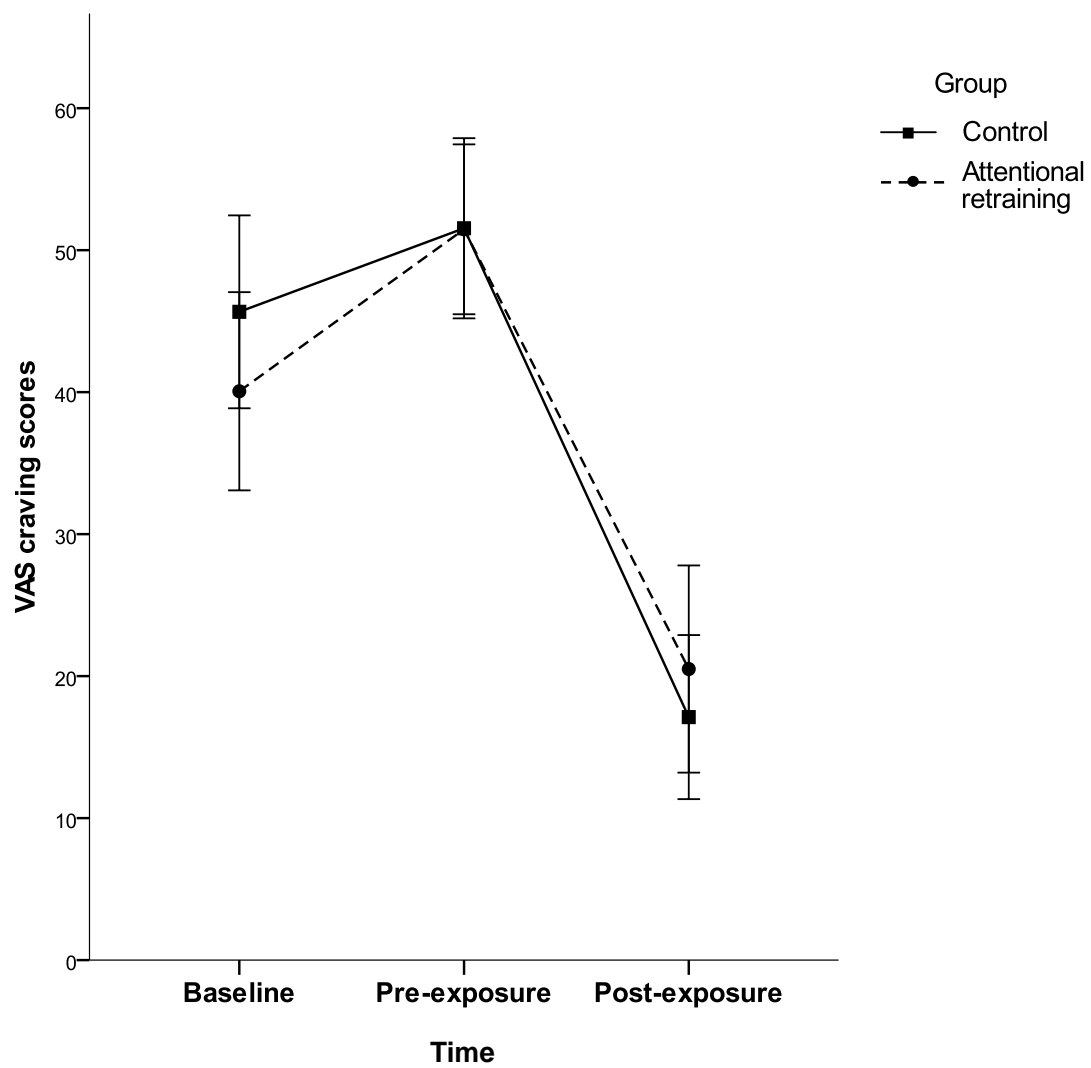
Linear combinations of the coefficients derived from the fully specified model indicated that there was a non-significant reduction in craving at pre-exposure and post-exposure at each block length in the AR group compared to the control group (Table 9). Irrespective of block length, craving scores at pre-exposure were 0.05 points less in the AR group than in the control group and 4.15 points less at post-exposure, although these differences did not reach statistical significance at either time point ( $ps>0.05$ ).

**Table 9. Linear combinations of coefficients for QSU-Brief scores at pre-exposure and post-exposure by short, medium and long block length**

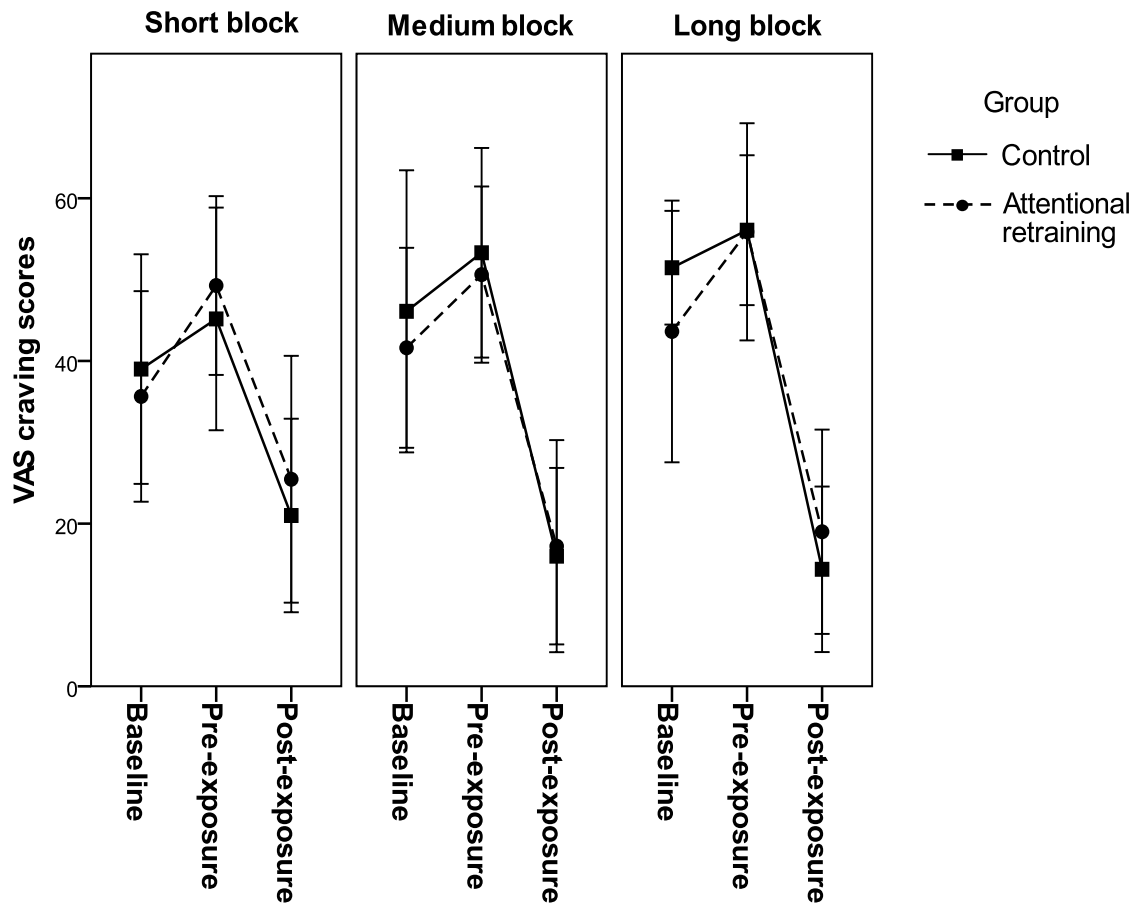
	Time					
	Pre-exposure			Post-exposure		
	Regression coefficient	p	CI	Regression coefficient	p	CI
Short	-0.05	0.99	(-10.03, 9.94)	-4.15	0.42	(-14.14, 5.84)
Medium	-2.05	0.69	(-12.12, 8.01)	-0.70	0.89	(-10.76, 9.36)
Long	-1.65	0.76	(-12.41, 9.10)	-3.84	0.48	(-14.59, 6.92)

#### 2.3.6.1.1 VAS

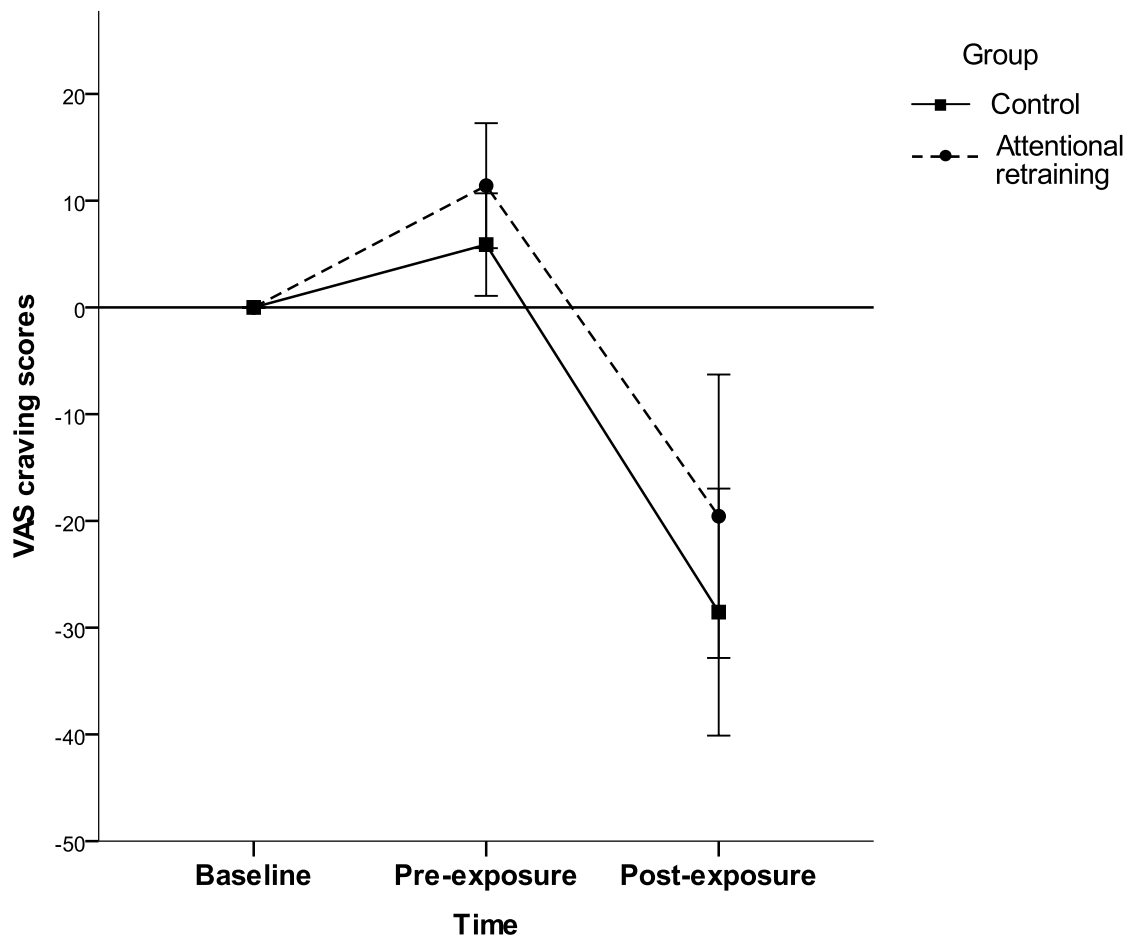
Mean scores for the VAS item “craving a cigarette” indicate that cue-induced craving increased from baseline to pre-exposure in both groups (Figure 8) and at each block length (Figure 9). There was a decrease in VAS scores from pre-exposure to post-exposure across both groups and at each block length. While the change in craving from baseline to pre-exposure was greater in the AR group compared to the control group (mean difference=5.52), the change in craving was less from pre-exposure to post-exposure (mean difference=3.46, see Figure 10). This was also evident across block lengths (Appendix 9).



**Figure 8. Mean (95% CI) VAS craving scores at baseline, pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35)**



**Figure 9.** Mean (95% CI) VAS craving scores at baseline, pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35) by short, medium and long block length



**Figure 10. Mean (95% CI) change in VAS craving scores from baseline to pre-exposure and post-exposure in the attentional retraining group (n=32) and control group (n=35)**

The mixed-effects model fitted to the data indicated that there were no significant three-way interactions between group, time and block length or two-way interactions of group by block length or group by time (Table 10). The most parsimonious model of VAS scores contained a significant time (post-exposure) by block length (long) interaction only, which suggests that there was no difference in trend across groups (Figure 9).

**Table 10. Mixed-effects models of VAS craving scores over time by group and block length**

Variable	Model 1		Model 2		Model 3		Model 4	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects								
Group <sub>1</sub>	-3.36	0.65	-2.93	0.60	-5.11	0.25	-0.41	0.87
Time (pre-exposure) <sub>2</sub>	6.17	0.41	7.08	0.25	7.08	0.25	9.74	0.07
Time (post-exposure) <sub>2</sub>	-18.00	0.01	-18.32	0.003	-18.32	0.003	-14.26	0.007
Block length (medium) <sub>3</sub>	7.10	0.35	8.55	0.16	6.62	0.21	6.21	0.24
Block length (long) <sub>3</sub>	12.46	0.08	11.90	0.05	10.59	0.05	11.04	0.04
Intercept	39.00		38.79		39.83		37.59	
Interactions								
Time (pre-exposure) x Block length (medium)	1.03	0.93	-2.00	0.79	-2.01	0.79	-1.52	0.84
Time (pre-exposure) x Block length (long)	-1.55	0.88	-1.67	0.83	-1.67	0.83	-2.22	0.78
Time (post-exposure) x Block length (medium)	-12.10	0.26	-13.35	0.07	-13.35	0.08	-12.61	0.09
Time (post-exposure) x Block length (long)	-19.08	0.06	-17.25	0.02	-17.25	0.03	-18.07	0.01
Group x Time (pre-exposure)	7.47	0.49	5.55	0.38	5.56	0.38		
Group x Time (post-exposure)	7.82	0.46	8.50	0.18	8.50	0.18		
Group x Block length (medium)	-1.12	0.92	-3.75	0.53				
Group x Block length (long)	-4.47	0.68	-2.89	0.64				
Group x Time (pre-exposure) x Block length (medium)	-5.67	0.71						
Group x Time (pre-exposure) x Block length (long)	0.16	0.99						
Group x Time (post-exposure) x Block length (medium)	-2.10	0.89						
Group x Time (post-exposure) x Block length (long)	4.63	0.77						

Table 10 continued

Variable	Model 1		Model 2		Model 3		Model 4	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Random effects								
Participant ID, intercept (SD)	1.23E-10		1.51E-10		1.12E-11		9.42E-11	
-2*log likelihood	-864.83		-864.99		-865.2		-866.15	

*Model 1: craving score by group, time, block length and interaction terms group x time x block length, group x time, group x block length, time x block length*

*Model 2: craving score by group, time, block length and interaction terms group x time, group x block length, time x block length*

*Model 3: craving score by group, time, block length and interaction terms group x time, time x block length*

*Model 4: craving score by group, time, block length and interaction term time x block length*

*<sub>1</sub> Reference category is control group, <sub>2</sub> Reference category is time (baseline), <sub>3</sub> Reference category is block length (short)*



Linear combinations of the coefficients indicated that at pre-exposure, there was a non-significant increase in craving for participants who received the short block length in the AR group compared to the control group, while a non-significant reduction was found in those that received the medium and long block lengths (Table 11). At post-exposure, across all block lengths, there was a non-significant increase in craving in the AR group compared to the control group, although the confidence intervals were again wide, indicating some degree of imprecision in the estimates.

**Table 11. Linear combinations of coefficients for VAS craving scores at pre-exposure and post-exposure by short, medium and long block length**

	Time					
	Pre-exposure			Post-exposure		
	Regression coefficient	p	CI	Regression coefficient	p	CI
Short	4.11	0.58	(-10.53, 18.74)	4.45	0.55	(-10.18, 19.09)
Medium	-2.68	0.72	(-17.43, 12.06)	1.23	0.87	(-13.52, 15.98)
Long	-0.20	0.98	(-15.96, 15.55)	4.61	0.57	(-11.14, 20.37)

### ***2.3.7 Effects of attentional retraining on mood and withdrawal***

Mood and withdrawal scores for STAI-State anxiety and VAS items “happy”, “drowsy”, “depressed”, “anxious”, “energetic” and “irritable” were analysed using mixed model 2 x 3 ANOVAs with group (attentional retraining/control) as the between-subjects factor and time (baseline/pre-exposure/post-exposure) as the within-subjects factor. There were significant main effects of time on VAS scores for the items “happy” ( $F[2,130]=12.12$ ,  $p<0.001$ , partial  $\eta^2=0.16$ ), “depressed” ( $F[2,130]=50.29$ ,  $p<0.001$ , partial  $\eta^2=0.44$ ), “anxious” ( $F[2,130]=6.23$ ,  $p<0.008$ , partial  $\eta^2=0.09$ ) and “irritable” ( $F[2,130]=6.75$ ,

$p < 0.006$ , partial  $\eta^2 = 0.09$ ). Scores for the items “anxious” and “irritable” increased over the three time-points, where as scores for “happy” decreased over time. Scores for “depressed” decreased from baseline to pre-exposure but increased from pre-exposure to post-exposure. No other main effects or interactions were significant ( $F_s < 5.42$ ,  $p_s > 0.01$ ).

When block length was included as an additional between-subjects factor in the model above, there were significant main effects of time for the items “happy” ( $F[2,122] = 13.07$ ,  $p < 0.001$ , partial  $\eta^2 = 0.18$ ), “depressed” ( $F[2,122] = 501.06$ ,  $p < 0.001$ , partial  $\eta^2 = 0.45$ ), “anxious” ( $F[2,122] = 6.83$ ,  $p < 0.005$ , partial  $\eta^2 = 0.10$ ) and “irritable”  $F[2,122] = 6.33$ ,  $p < 0.008$ , partial  $\eta^2 = 0.09$ ) and a time x block length interaction for “happy”  $F[2,122] = 7.49$ ,  $p < 0.001$ , partial  $\eta^2 = 0.20$ ). There was a general decrease over time for ratings of “happy” across block length, apart from at the long block length where there was an increase from pre-exposure to post-exposure. Mean scores for “depressed”, “anxious” and “irritable” increased over time.

For STAI-State anxiety scores, there was a significant increase over time ( $F[2,110] = 27.77$ ,  $p < 0.001$ , partial  $\eta^2 = 0.34$ ) but no other significant main effects or interactions were found ( $F_s < 0.60$ ,  $p_s > 0.51$ ). With the inclusion of block length (short, medium, long) as a between-subjects factor in the ANOVA above, there were main effects of time ( $F[2,102] = 27.32$ ,  $p < 0.001$ , partial  $\eta^2 = 0.35$ ) and block length ( $F[2,51] = 3.51$ ,  $p < 0.04$ , partial  $\eta^2 = 0.12$ ), while all other interactions were not significant ( $F_s < 1.42$ ,  $p_s > 0.25$ ). Post-hoc tests revealed that anxiety scores were higher for those who

received the long block length than those who received the short block length (mean difference=7.19) and this difference approached significance ( $p=0.07$ ).

### ***2.3.8 Effects of attentional retraining on pictorial Stroop task performance***

An independent sample t-test revealed that there was no significant difference between groups in Stroop bias scores post-training ( $t[65]=1.25$ ,  $p=0.22$ ). See Table 12 for summary data.

To examine whether there were group differences in colour-naming RT scores to each picture type, data were analysed using a 2 x 2 mixed model ANOVA with group (attentional retraining/control) as the between-subjects factor and picture type (smoking-related pictures/neutral pictures) as the within-subjects factor. No significant main effects or interactions were observed ( $F_s < 1.57$ ,  $p_s > 0.22$ ), which suggests that attentional retraining had no effect on Stroop task performance. This was also the case when block length (short, medium, long) was added as an additional between-subjects factor in the ANOVA above ( $F_s < 2.62$ ,  $p_s > 0.08$ ).

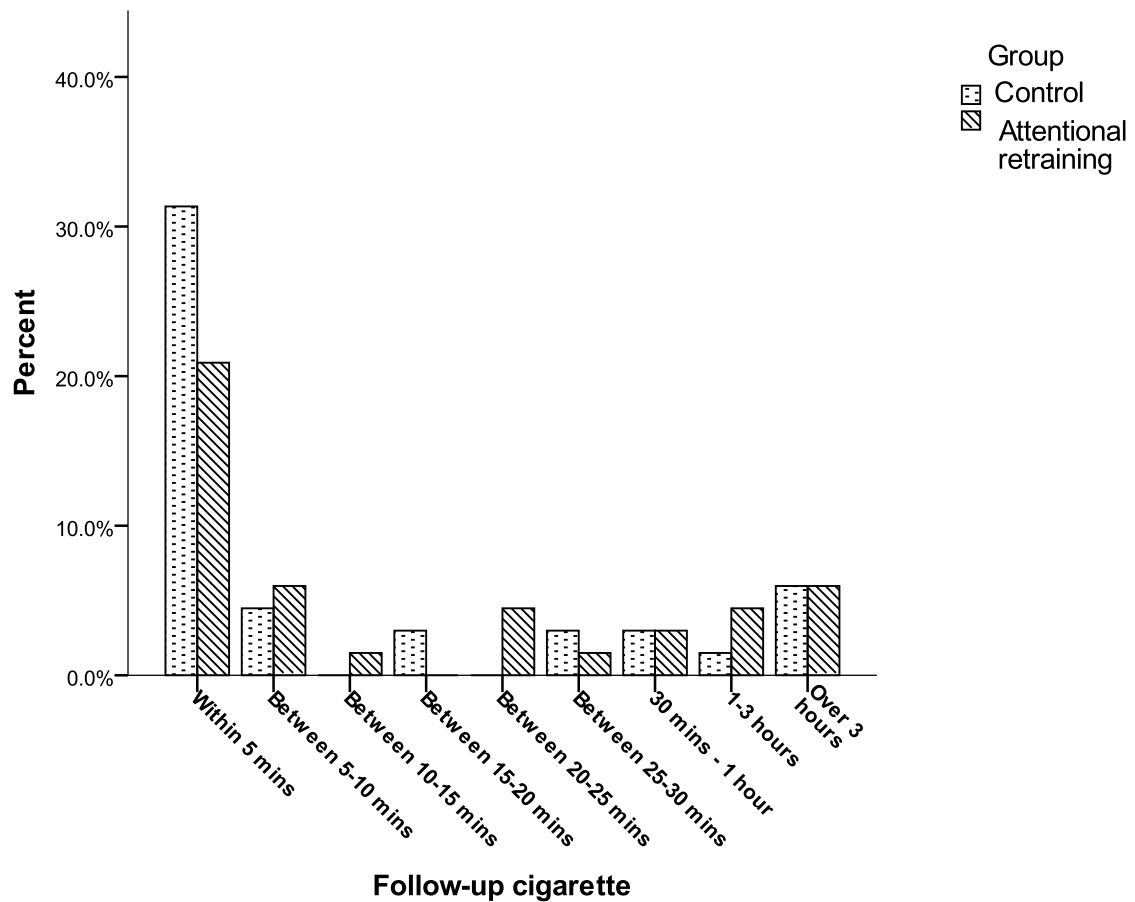
**Table 12. Pre-training and post-training Stroop bias scores by group**

	Attentional retraining (n= 32)	Control (n=35)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
RT for smoking stimuli	735.55 (160.66)	692.11 (155.09)	43.43	1.13	0.26	(-33.63, 120.50)
RT for neutral stimuli	707.66 (135.35)	694.03 (110.25)	13.63	0.45	0.65	(-46.39, 73.64)
Stroop bias	27.89 (75.40)	-1.91 (113.75)	29.80	1.25	0.22	(-17.75, 77.36)

*RT - reaction time (milliseconds)*

### ***2.3.9 Effects of attentional retraining on time to first cigarette after laboratory session***

The majority of participants reported having a cigarette within 5 minutes of leaving the laboratory session; this number was higher in the control group (60%) than the AR group (43.8%, see Figure 11). Overall, there were no significant differences between groups in the time to first cigarette ( $U=472.50$ ,  $p=0.24$ ,  $r=0.15$ ).



**Figure 11. Time to first cigarette following laboratory session in the attentional retraining group (n=32) and control group (n=35)**

### **2.3.10 Contingency awareness**

In total, 14 participants (20.9%) were ‘aware’ of the experimental contingency (i.e. they had correctly identified the relationship between the location of the probe and picture type or lack thereof in the case of the control group). The remaining 53 participants (79.1%) were ‘unaware’ of the experimental contingency (i.e. they had incorrectly identified the relationship between the location of the probe and picture type or were unsure). There was a significant association between group and contingency awareness ( $\chi^2=11.70$ ,  $p<0.001$ ), where significantly fewer participants in the AR group (n=1, 3.1%) were ‘aware’ of the

experimental contingency in comparison to the control group ( $n=13$ , 37.1%). Due to the low number of participants who were aware of the experimental contingencies in the AR group, we were unable to carry out any further analyses on the role of contingency awareness on the effects of AR.

### ***2.3.11 Effect of block length on error rate***

Table 13 shows summary data for the number of errors made during training trials by each block length. Multilevel logistic regression indicated that compared to those who received the short block length, participants were more likely to make errors if they received the medium block length (OR 1.55, 95% CI=0.72, 3.35). The risk of making an error increased if participants received the long block length (OR 2.03, 95% CI=0.93, 4.42). However, statistical significance was not reached in either case ( $p>0.07$ ).

**Table 13. Number of errors made by short, medium and long block length**

	Short ( $n=2208^*$ )	Medium ( $n=4416^*$ )	Long ( $n=5526^*$ )
Incorrect responses (% of total)	68 (0.6)	195 (1.6)	243 (2.0)
<200 RT	13 (0.1)	51 (0.4)	26 (0.2)
>1500 RT	18 (0.1)	26 (0.2)	50 (0.4)

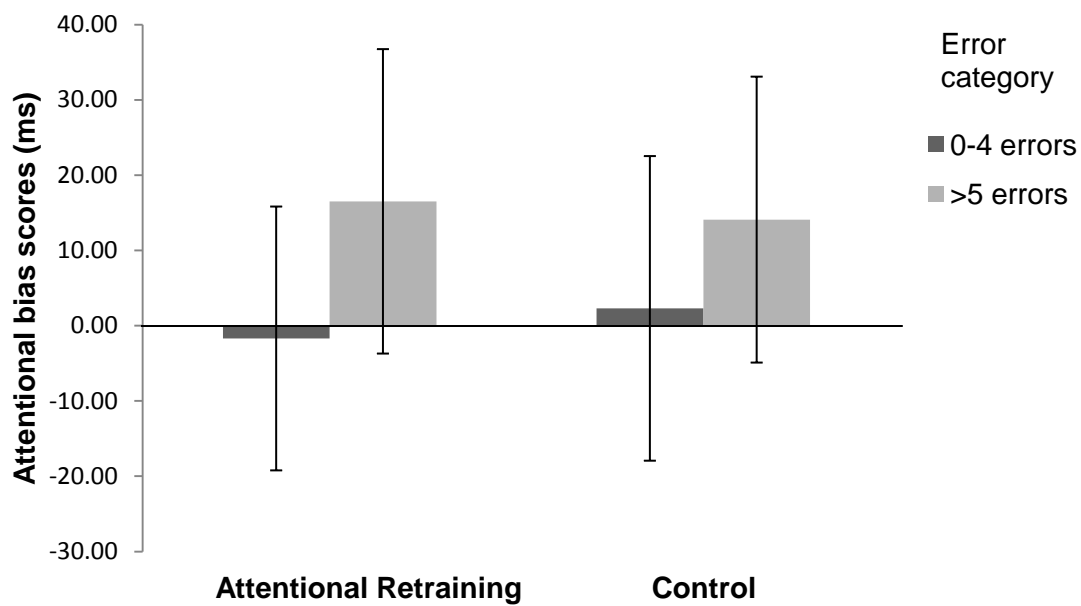
\*Total number of trials across all participants

### ***2.3.12 Error frequency on attentional retraining effects***

To examine whether error frequency was a mediator of retraining effects, linear regression was carried out with error as an explanatory variable and post-training attentional bias score as the outcome variable. Pre-training attentional bias scores were

controlled for in the analysis. Prior to analysis, a categorical variable was created for errors made because the distribution of errors was positively skewed. Error was split into two categories: 0-4 errors and >5 errors. There were too few participants in each category to explore interactions by block length, therefore block length was omitted from the model and the subsequent analysis was performed by group only.

In participants who made less than five errors during training trials, a reduction in post-training attentional bias scores was found in the AR group compared to the control group ( $\beta=-4.00$ ,  $p=0.77$ , 95% CI=-31.32, 23.32), while an increase was found in those who made more than five errors ( $\beta=2.43$ ,  $p=0.86$ , 95% CI=-25.87, 30.72). Attentional retraining effects appeared to decrease as the frequency of errors made during training trials increased (Figure 12), however we should note that there were no significant main effects or interactions ( $ps>0.39$ ) and the reported coefficients were small and encompassing confidence intervals wide.



**Figure 12. Attentional bias scores (ms) by error frequency in the attentional retraining group (n=32) and control group (n=35)**

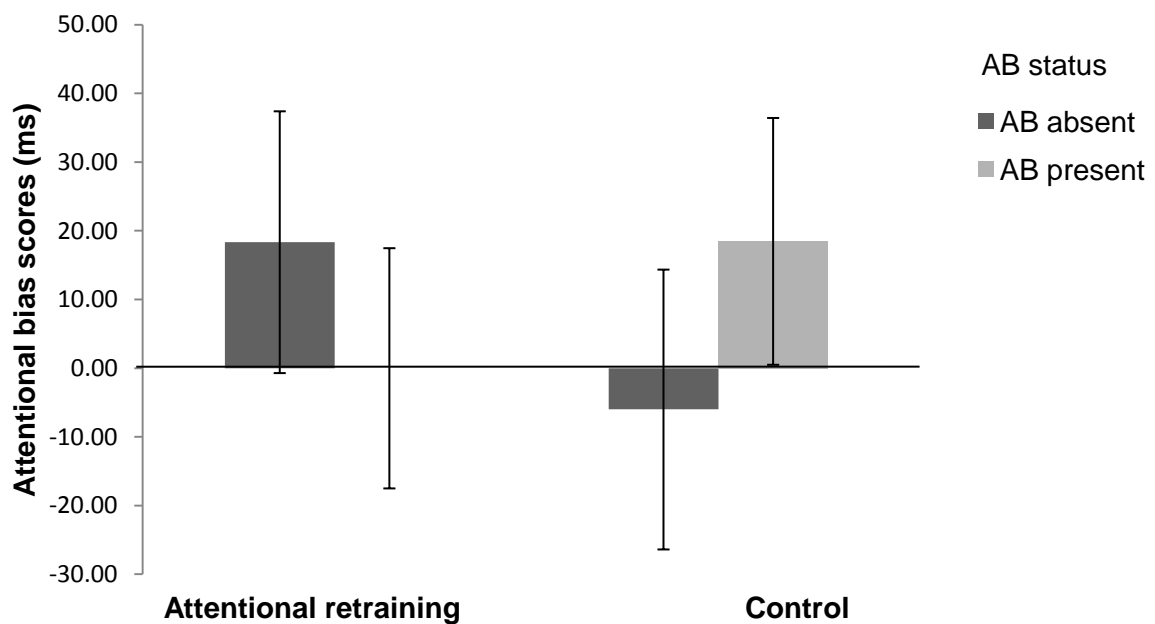
### 2.3.13 Sub-group analyses

As the sample did not exhibit an attentional bias towards smoking-related stimuli at baseline, we explored whether retraining effects were seen in those who did exhibit an attentional bias at baseline. A categorical variable was created which specified whether attentional bias was absent or present at baseline; a positive RT score indicated that attentional bias was present ( $RT > 0$ ), while a negative score indicated that attentional bias was absent ( $RT < 0$ ). As block length had little influence on treatment outcome as demonstrated in the primary analysis, this variable was omitted from the sub-group analyses.



### 2.3.13.1 Effect of attentional bias absence/presence on post-training attentional bias scores

Linear regression was performed with attentional bias absent/present as an explanatory variable to predict post-training attentional bias scores. The analysis indicated that post-training attentional bias scores were 24.36 ms higher in participants who did not have an attentional bias at baseline in the AR group compared to the control group ( $p=0.09$ ). In participants who had an attentional bias at baseline, there was an 18.47 ms reduction in post-training attentional bias scores in the AR group compared to the control group ( $p=0.15$ , see Figure 13).



**Figure 13.** Post-training attentional bias scores (ms) by attentional bias absence/presence at baseline in the attentional retraining group (n=32) and control group (n=35)

### *2.3.13.2 Effect of attentional bias absence/presence on subjective craving*

To explore the influence of baseline attentional bias on subjective craving, an attentional bias absent/present variable was added to the parsimonious model of QSU-Brief scores. This model was used in preference to the fully specified model to reduce the risk of over-fitting and making the model unstable. Three-way and two-way interactions between group, time and attentional bias absent/present were included. This model was used to produce linear combinations of the coefficients to compare groups.

The analysis indicated that there were no significant three-way or two-way interactions ( $p>0.77$ ). At pre-exposure, QSU-Brief scores were 3.79 points less in participants who had an attentional bias at baseline in the AR group compared to the control group, while an increase of 5.06 points was found in those who had no attentional bias at baseline. A similar pattern was found at post-exposure in those with attentional bias ( $\beta=-4.76$ ) and without attentional bias ( $\beta=0.35$ ). However, at neither time point were these coefficients significant ( $ps>0.2$ ), most probably due to the lack of statistical power.

## **2.4 Discussion**

### *2.4.1 Summary of principal findings*

This laboratory study evaluated the impact of varying the length of AR on attentional bias and subjective craving in current smokers. Contrary to the findings of the previous study (Attwood et al., 2008), the AR intervention did not produce a significant decrease in attentional bias for smoking-related cues irrespective of the length of training given.

Both QSU-Brief and VAS craving measures were highly correlated with each other, although neither measure correlated with attentional bias scores. There was no significant difference in subjective craving between groups at each block length on either measure, however there was some indication of an overall reduction in QSU-Brief scores in the AR group following cue exposure.

There was no difference in mood and withdrawal ratings between groups. Across block lengths, anxiety scores were higher in participants who received the long block length in comparison to those that received the short block length, although this only approached significance.

We observed no retraining effect on other measures of cognitive bias (the pictorial Stroop task), either by group or block length. There were no effects of training on indirect behavioural measures, i.e. the time it took participants to have their first cigarette after leaving the laboratory session.

We found that the likelihood of making an error during training trials increased as the length of the training block increased. We further found tentative evidence that retraining effects on attentional bias were influenced by the number of errors made during training trials. Post-training attentional bias scores were lower among trained participants who made fewer errors during training trials compared to control participants; the reverse was

true for trained participants who made more errors, with bias scores being higher relative to control participants.

Perhaps the most unexpected finding was that the sample did not exhibit a significant attentional bias at baseline. There was some indication that retraining effects were contingent on whether participants exhibited an attentional bias at baseline; we found tentative evidence of a reduction in attentional bias among trained participants who had an attentional bias at baseline compared to control participants. The effects of retraining in this subgroup of participants extended to non-significant reductions in craving immediately after retraining and following cue exposure. We should note, however, that these findings are exploratory in nature and should be interpreted with some caution, as discussed below.

#### ***2.4.2 The findings in the context of previous studies***

While we were unable to replicate the findings of the Attwood et al. (2008) study, this study provides partial support for other tobacco-related retraining studies (Field et al., 2009b; McHugh et al., 2010). In the study by Attwood et al. (2008), significant reductions in attentional bias towards smoking cues were observed in a train-to-avoid group, while increases in attentional bias and craving were found in a train-to-attend group. Field et al. (2009b) replicated the study with the inclusion of a control group and found a decrease in attentional bias in the avoid group, but this failed to reach statistical significance; in fact, training effects appeared to be more robust in the group trained to attend to smoking cues. Furthermore, no effects on urge to smoke were found in either group. Perhaps most

similar to the findings of our study is the study by McHugh et al. (2010) who found no retraining effects on attentional bias or craving in participants trained to avoid smoking cues. We found that AR did not significantly reduce attentional bias for smoking cues or induce an attentional bias away from smoking cues in the AR group.

There are several possible reasons why this study and the aforementioned studies were unable to detect a significant reduction in attentional bias from train-to-avoid experimental manipulations. Primarily, this could be because most retraining studies differ in design and the groups used for comparison. In both tobacco and alcohol-related retraining studies carried out in non-clinical samples, successful retraining effects have been reported in studies that compared attend with avoid manipulations (Attwood et al., 2008; Field & Eastwood, 2005) or where larger samples have been used (Schoenmakers et al., 2007). Studies that used a control comparison, like our study, have either found no retraining effect on attentional bias in the avoid group (McHugh et al., 2010) or weaker effects in the avoid groups in comparison to the attend groups (Field et al., 2007b; Field et al., 2009b). Given that it is likely that attentional bias occurs after long-term exposure to drug-related stimuli (Robinson & Berridge, 1993; Robinson & Berridge, 2001), it is perhaps more difficult for smokers to break a conditioned response to smoking cues with a train-to-avoid manipulation than it is to train individuals to attend to an existing bias. Moreover, as discussed by Wiers et al. (2006), the difference in attentional bias scores between two experimental manipulations (i.e. attend and avoid) is larger than the difference between a control comparison and an experimental manipulation. Taken together, it would seem that retraining effects are harder to achieve in avoid groups rather

than attend groups and where comparisons are made with a control group. If the effect of AR is indeed small, larger sample sizes may be required to detect a robust effect.

Consistent with the findings from other studies (Field et al., 2009b; McHugh et al., 2010; Schoenmakers et al., 2007), retraining effects on subjective craving were small in this study. Although there was some suggestion that craving reduced over cue exposure, the effects were negligible. Causal associations between attentional bias and subjective craving are often described as weak and inconsistent across tobacco and alcohol-related studies (Field et al., 2009a); any observed effects of retraining have been constrained to participants with certain characteristics, i.e. in males (Attwood et al., 2008) and those only aware of the experimental contingency (Field et al., 2007b). Again, retraining effects on subjective outcomes were only seen in the attend groups and did not extend to the avoid groups. We did not find any differential retraining effects by gender, or awareness of the experimental contingency. In fact, the number of ‘aware’ participants was too small to investigate this. This finding is similar to the Field et al. (2009b) study in that very few participants were contingency aware and so it remains to be explored whether making people aware of the experimental contingency could enhance the training effect. Future studies should investigate this possibility as awareness of the training manipulation has been particularly relevant in observing the predicted changes in subjective craving (Attwood et al., 2008; Field et al., 2007b).

Unexpectedly, VAS craving scores decreased across both groups during cue exposure. Previous studies have found that VAS craving scores generally increase over time

(Attwood et al., 2008), although we are unable to explain why this pattern was not observed in this study.

Another major difference between this study and others is that the amount of AR given to participants was much less than what has been provided in other retraining studies (see Table 1). Retraining effects were observed in studies where twice as many trials were used during training than in the present study. For example, Attwood et al. (2008) used a total of 512 retraining trials to detect significant effects between their groups, while in our study the shortest length consisted of 96 trials and the longest length, 196 trials.

Additionally, the longest block length of training was no more effective than the shortest block length. We might consider from our findings that a single session of AR at the block lengths explored in this study may not have been sufficient to produce the desired change in attentional bias or subjective craving.

We initially opted for shorter training blocks in view of using this procedure in a clinical setting where practitioners not only have time-constraints on the duration of consultations, but patients may not adhere well to treatments given in lengthy sessions. Indeed, we found in the present study that increasing the block length increased the likelihood of errors being made during training trials, suggesting that participants experienced boredom or attentional fatigue as the length of training increased. Arguably, this may not be the case in patients that are actively seeking treatment, as they may be more engaged in the task if they thought that it was helping them overcome their addiction. There was some indication from our findings that making more errors may have reduced the effectiveness

of AR as evidenced in post-training attentional bias scores, although we were unable to explore this association by block length due to the low number of participants. It may be of interest in future investigations to explore the impact of error frequency on retraining effects at longer block lengths and in larger samples.

It is important to note, however, that simply increasing the number of training trials may not be sufficient to affect clinical outcomes. Previous studies that have used a single session of training have often been unable to detect retraining effects on behavioural outcomes; for example, Attwood et al. (2008) found no retraining effects on smoking topography and Field et al. (2009b) found no effect on tobacco-seeking motivation or smoking rate. Similarly, effects have been inconsistent across alcohol-related retraining studies (Field et al., 2007b). However, studies using multiple sessions of AR have found some evidence for effects on drug-seeking behaviour. In Schoenmakers et al. (2010) alcohol-dependent patients who were trained to avoid alcohol cues over an extended period of time in five sessions were not only discharged from their treatment facility sooner than the control group, but they also remained abstinent for longer than their counterparts. In Fadardi and Cox (2009), harmful drinkers significantly reduced their weekly alcohol consumption after receiving four sessions of training and these reductions were maintained three months later. To this end, several authors suggest that increasing the frequency of training sessions may be necessary to produce long-lasting changes in attentional bias, rather than task-specific changes (Field et al., 2009b; McHugh et al., 2010). For AR to be clinically effective, global changes in attentional bias are required if attentional bias does in fact underpin subjective craving and tobacco-seeking behaviour; multiple sessions may be the way forward to achieve this.



Studies that used multiple sessions in their design also differed from this study in respect of the samples recruited. As this was a laboratory study designed to inform our clinical trial, we recruited a sample of non-treatment seeking smokers. There may be differential effects of training by the population group targeted; preliminary evidence for this comes from Fadardi and Cox's (2009) study, where harmful and hazardous drinkers – who were interested in reducing their consumption - demonstrated a bigger reduction in cognitive bias following training than social drinkers. Retraining may have more of an effect in smokers who are motivated to abstain or seeking smoking cessation. Additionally, we found some indication that retraining effects on attentional bias were contingent on whether attentional bias was present in participants at baseline. A further consideration is that participants were relatively light smokers (as evidenced by their low FTND scores) and so it is unclear whether the effects of retraining are more pronounced in heavier smokers. Taken together, it may be that attentional bias is only present in individuals who possess certain characteristics or that retraining effects are mediated by factors such as smoking status, nicotine dependence or smoking rate. Identifying these individual characteristics and the potential moderators of AR are therefore of particular importance in large-scale studies, in order to establish who would be most receptive of and benefit from this type of treatment.

Finally, we found no effect of AR on selective processing biases assessed on a different task measure – participants were not slower to identify the colour of the border of the neutral pictures compared to the smoking-related pictures on the Stroop task. This is consistent with other studies that have assessed generalisation to the Stroop task (Field et al., 2007b; Field et al., 2009b). We should perhaps be cautious in our interpretation of this

finding as no pre-training measure of Stroop bias was taken, and so future studies that assess generalisation should include this as a baseline assessment.

### ***2.4.3 Implications for the ARTS trial***

The purpose of the present study was to explore how much attentional retraining would be required to produce an effect on attentional bias and craving for use in a clinical setting as a therapeutic intervention. Another purpose was to explore whether boredom/fatigue occurred with more training given, characterised by the number of errors made, and if the number of errors made had any impact on retraining effects.

Taking these preliminary findings from this study into consideration, as well as the points from the discussion above and the context in which the intervention will be delivered, we have made the following recommendations on the design of our clinical trial.

- 1) We considered that the AR intervention needed to be of a length that was both acceptable to patients and practical for stop smoking practitioners to deliver within a reasonable time-frame in a typical stop smoking clinic. A single session of AR at either of the three block lengths explored in this study did not produce a significant reduction in attentional bias or subjective craving, and so our decision was made on other factors. As there was some indication that anxiety was higher in those who received the long block length and that more errors were made as the length of the training block increased, the long block length was subsequently

disregarded. There appeared to be little difference in retraining effects between one block and two blocks of training; a decision was made to use two blocks of training, with the condition that this was separated by a break in which the practitioner would deliver behavioural support between blocks to minimize attentional fatigue.

- 2) Successful retraining effects on attentional bias and drug-seeking behaviour have been found in cases where multiple sessions of training were used in dependent populations (Fadardi & Cox, 2009; Schoenmakers et al., 2010). We have similarly chosen to use multiple sessions of training, which was considered a more practical way of increasing the ‘dose’ of training given to patients, and avoided the need to extend the length of each stop smoking clinic session. Five sessions of AR were chosen to be delivered weekly, to fit in line with the standard 7-week NHS stop smoking programme.
- 3) Although retraining effects in this study did not generalize to the Stroop task, we decided to re-assess this in our clinical trial, in this case with a baseline assessment included (see Chapter 3 for description).

# **CHAPTER 3: A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL OF ATTENTIONAL BIAS RETRAINING IN CIGARETTE SMOKERS ATTEMPTING SMOKING CESSATION (ARTS) – PROTOCOL**

## **3.1 Introduction**

The reporting of the ARTS trial spans Chapters 3, 4 and 5. The present chapter describes the protocol for the trial, which has been published (Begh et al., 2013; Appendix 10). It specifically outlines the objectives of the study and the methods undertaken.

### ***3.1.1 Rationale for the trial***

As discussed in section 1.1, resumption of smoking by initially successful quitters is arguably the greatest public health challenge in smoking cessation. While there are few interventions at present that are known to reduce the risk of relapse to smoking (Hajek et al., 2009), the development of new approaches like attentional retraining could be worthwhile. Despite evidence from laboratory studies indicating that attentional bias can be modified in cigarette smokers using AR procedures (Attwood et al., 2008; Field et al., 2009b) and the success of such tasks on improving clinical outcomes in other addictions (Schoenmakers et al., 2010) and psychopathologies (Amir et al., 2009a), at the time of writing no study had yet examined the clinical application of such procedures in treatment-seeking smokers.

We therefore carried out a pilot double-blind randomised controlled trial of multiple sessions of attentional bias retraining in smokers attempting smoking cessation (ARTS). This translational study offered the ability to both examine the benefits of AR on users of NHS stop smoking services and provide data to aid our understanding on the phenomenon of attentional bias and its relation to craving, withdrawal symptoms, lapses and relapse in smokers attempting to quit. The trial was designed as a pilot study to test both the feasibility and acceptability of the ARTS intervention, upon which to inform a larger trial.

### **3.1.2 Objectives**

- 1) To investigate the feasibility of delivering an attentional retraining intervention within NHS stop smoking services and explore the acceptability of the procedures to service-users;
- 2) To investigate the efficacy of an attentional retraining intervention on attentional bias and smoking cessation outcomes;
- 3) To investigate the association between attentional bias, urges to smoke, withdrawal and relapse in smokers.

In the following section I describe the study questions that were developed to answer the main objectives of the study, in light of the literature reviewed in Chapter 1.

### 3.1.3 *Study questions*

- 1) Are attentional retraining procedures feasible to deliver within NHS stop smoking services and are they acceptable to smokers seeking cessation support?

While the primary objective of many attentional retraining studies has been to examine the efficacy of AR, most have often neglected to report on the processes involved in delivering these procedures in a clinical setting. Additionally, very little is known on whether patients themselves accept and adhere to this form of treatment. As the ARTS trial involved a new intervention being delivered in an established service, it was necessary to examine the feasibility of running the trial in practitioner-led NHS stop smoking clinics and to also assess the acceptability of the procedures to NHS patients.

- 2) Can attentional retraining diminish attentional bias in smokers during cessation; are the effects evident across different cognitive bias tasks and different types of stimuli?

As evidenced in the laboratory studies discussed in section 1.3, individuals with specific drug use patterns have shown increases or decreases in attentional bias towards their drug of choice by using modified versions of the visual probe task (Attwood et al., 2008; Field & Eastwood, 2005; Field et al., 2007b; Field et al., 2009b; Schoenmakers et al., 2007). Attentional retraining has led to reductions in attentional bias towards alcohol cues and delayed time to relapse in alcohol-dependent patients seeking treatment for alcohol abuse (Schoenmakers et al., 2010). Evidence from two laboratory studies in non-treatment seeking smokers demonstrated that a train-to-avoid manipulation of smoking cues could reduce attentional bias in non treatment-seeking smokers in a single session (Attwood et

al., 2008; Field et al., 2009b). We thus chose to investigate whether AR – using multiple sessions - could lead to similar reductions in attentional bias in smokers who were attempting cessation. If retraining were successful, participants would be able to demonstrate that they can divert their attention away from smoking cues on the visual probe task. We would expect AR to reduce the degree to which smokers notice smoking cues in their environment because they are trained away from attending to them.

Similarly, if AR showed material reductions on one cognitive bias task, it is plausible that a reduction may be seen on another task measure - such as the pictorial Stroop task - if similar attentional processes were involved. Finally, if AR were able to produce a global change in attentional bias and not just a task-specific change in bias towards smoking cues, then smokers should be able to transfer their ability to disengage their attention to other smoking cues that are not featured in the retraining procedure.

3) Does attentional retraining affect urges to smoke, cue-induced craving or withdrawal symptoms in smokers during cessation?

Previous studies have revealed mixed findings on the effects of AR on craving and withdrawal. As I reviewed in section 1.4.2, some experimental paradigms have successfully increased attentional bias towards smoking-related cues or alcohol-related cues and found a corresponding increase in cue-induced craving (Attwood et al., 2008) or urge to drink (Field & Eastwood, 2005; Field et al., 2007b), respectively. On the other hand, AR has often had no effect on craving, mood and withdrawal in train-to-avoid manipulations (Attwood et al., 2008). However, as highlighted in section 1.6,

motivational processes could differ between continuing smokers and treatment-seeking smokers. Therefore, we investigated the effects of AR on urges to smoke, cue-induced craving and withdrawal symptoms in smokers during their cessation attempt. If AR procedures are capable of reducing exposure by diverting attention away from smoking cues, this in turn could reduce the capacity of these cues to invoke craving and symptoms of withdrawal.

- 4) Do the effects of attentional retraining on attentional bias persist up to 6 months after cessation?

The durability of AR remains unclear at present. Field et al. (2009b) found the predicted changes in attentional bias immediately after smokers were trained in a single session to attend or avoid smoking-related cues, but found that these effects disappeared in a second assessment session conducted one day later. One marker for the success of these procedures is to evaluate whether they produce enduring effects; this is particularly pertinent if the presence of attentional bias undermines abstinence (Powell et al., 2010). Accordingly, we investigated whether retraining effects were evident in smokers after their cessation attempt at follow-up assessments.

- 5) Does attentional retraining reduce the likelihood of relapse in smokers attempting cessation?

Preliminary investigations in alcohol-dependent populations have revealed clinically relevant effects of AR including earlier treatment discharge and delayed time to relapse



[(Schoenmakers et al., 2010) see section 1.7]. We therefore questioned whether retraining could reduce the likelihood of relapse in smokers attempting to quit. If the ability to train attention away from smoking-related cues during retraining translated to a smoker's natural environment, s/he might experience less exposure to the environmental cues that would normally trigger smoking; in time, this could weaken the stimulus-response association between smoking cues and smoking behaviour, thus reducing the likelihood of a lapse occurring. Alternatively, if attentional avoidance leads to less instances of craving (as hypothesised in the second study question) this also may in turn reduce the likelihood of relapse, given that craving predicts relapse (Waters et al., 2003a; Killen & Fortmann, 1997; Shiffman et al., 1997).

- 6) Do smokers who are attempting to quit exhibit an attentional bias towards smoking-related cues?

It is well-documented that drug-users show an attentional bias towards drug-cues of their choice (Field & Cox, 2008) but as I have discussed in section 1.7, some evidence from alcohol studies on attentional bias indicate that treatment-seekers or abstainers display attentional avoidance, that is, a bias *away* from alcohol-related cues (Noel et al., 2006; Townshend & Duka, 2007). To facilitate our understanding of the underlying mechanisms of attentional bias in smokers seeking to quit, we investigated whether treatment-seeking smokers show an attentional bias towards or away from smoking-related cues at baseline.

- 7) Is attentional bias related to the severity of nicotine dependence; is it also related to the severity of urges to smoke and withdrawal prior to and after quitting?

There is some evidence to suggest that the severity of dependence could be a modulating factor of attentional bias, although the direction of this relationship is currently unclear. On the one hand, some studies have found that heavily dependent smokers show greater reactivity to smoking-related cues than less dependent smokers (Vollstadt-Klein et al., 2011), while others have shown the opposite; for example Hogarth et al. (2003) found that light smokers (who smoked less than 20 cigarettes a day) had greater attentional bias than heavier smokers. In the former case, it is plausible that heavier smokers are more reactive to smoking cues as predicted by incentive salience theories (Robinson & Berridge, 1993) because greater exposure to cigarettes should lead to greater activation in the reward circuitry in the brain, in turn increasing sensitisation to smoking cues. In the latter case, less dependent smokers who consume fewer cigarettes may be more reactive as a result of developing greater stimulus control, presumably due to smoking in response to a narrower set of stimuli than heavier smokers (Hogarth et al., 2003; Watson et al., 2010). We chose to clarify these contradictory findings by examining the association between attentional bias and the severity of dependence in our sample of treatment-seekers.

In section 1.4, I described how several studies have attempted to explore the relationship between attentional bias and craving. The causal relationship between the two processes has been described as weak at best (Field et al., 2009a) with many experimental manipulations of attentional bias failing to find corresponding effects on craving (Field et al., 2009b; Schoenmakers et al., 2007). The design of the current study permitted us to explore this relationship by examining whether attentional retraining away from smoking-related cues could lead to reductions in craving.

Another aspect of this relationship that remains unclear is the association between attentional bias and the severity of craving and withdrawal. Evidence from alcohol studies indicates that higher levels of craving are predictive of higher levels of attentional bias in abstinent alcoholics (Field et al., 2012). In non treatment-seeking smokers, positive correlations have been found between attentional bias and craving (Kang et al., 2012). In treatment-seeking smokers, Waters et al. (2003c) found that those with higher craving at baseline had greater attentional bias than those with lower levels of craving, but this association was found on one half of the task but not on the other. In light of these tentative findings in treatment-seeking smokers, we chose to examine whether attentional bias was related to the severity of cravings and withdrawal during quit attempts.

8) Is attentional bias associated with an increased probability of relapse?

As discussed in section 1.5, there is some evidence indicating that attentional bias predicts relapse during quit attempts. Some tobacco-related studies have found that greater processing biases are associated with an increased risk of lapsing (Waters et al., 2003a) and relapse (Powell et al., 2010) while others have not (Spiegelhalder et al., 2011; Waters et al., 2003c). To clarify these findings and understand the prognostic value of attentional bias on the success of quitting, we investigated this association in our sample of smokers.

Questions 1-5 were addressed using the data from the study as trial data across both the trial arms, while questions 6-8 were explored by using the data as observational data.

## **3.2 Methods**

### **3.2.1 *Trial design***

This was a pilot double blind randomised controlled trial. Participants attending a 7-session weekly NHS stop smoking clinic were randomised to either an intervention group consisting of a modified visual probe task with attentional retraining (AR) or a control group with placebo training (PT). Five sessions of AR or PT were delivered.

### **3.2.2 *Inclusion criteria***

Participants were required to meet the following inclusion criteria to be eligible for enrolment into the trial:

1. Aged 18 years or over.
2. Smoked at least 10 cigarettes per day or 12.5 grams of tobacco or had a value of at least 10 parts per million (ppm) for exhaled carbon monoxide (CO).
3. Had normal or corrected-to-normal vision.
4. Showed evidence of a signed and dated informed consent document indicating that s/he had been informed of all aspects of the study and consented to participate and be randomised to either group.
5. Were able and willing to complete all study procedures.

### **3.2.3 *Exclusion criteria***

Participants were excluded if they presented with any of the following:

1. A medical condition that prevented them from seeing the computerised images properly, attending to the task, or pressing the keyboard buttons on the computer accurately, or completing any other study procedures.
2. Were currently using nicotine replacement therapy (NRT), bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture) that they were not willing to cease using and instead use study medication (i.e. nicotine patches as described in section 3.2.9.3.1).
3. Had previously had severe skin reactions to nicotine patches or severe eczema or other skin diseases that made patch use hazardous or undesirable.
4. Had a severe acute or chronic medical or psychiatric condition or previously diagnosed clinically important renal or hepatic disease, which could have increased the risk associated with study participation or could have interfered with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

#### **3.2.4 *Withdrawal criteria***

It is standard practice in smoking cessation trials to treat those who fail to attend appointments as having relapsed (West et al., 2005). Therefore, failure to attend was not defined as withdrawal from the trial; we considered that the only withdrawals would be those in which the participant had asked to be withdrawn. We expected this in less than 5% of participants. This is standard procedure in smoking cessation studies.

### **3.2.5 Participant recruitment**

Participants were recruited from West Midlands NHS SSS. A letter of invitation (Appendix 11) and a patient information sheet about the study (Appendix 12) were sent from GP practices to patients that were registered on their databases as smokers. The letters asked those patients who wished to take part in the trial to respond to the study team. In our experience, we anticipated that 5–10% would respond. In our later recruitment approaches described in Chapter 4, we approached staff within the NHS SSS to write to smokers on their database that had a history of failed quit attempts. Preliminary eligibility to participate was assessed during telephone screening (Appendix 13) and potential participants were booked in for an assessment session at the clinic site, similar to that arranged by the NHS SSS.

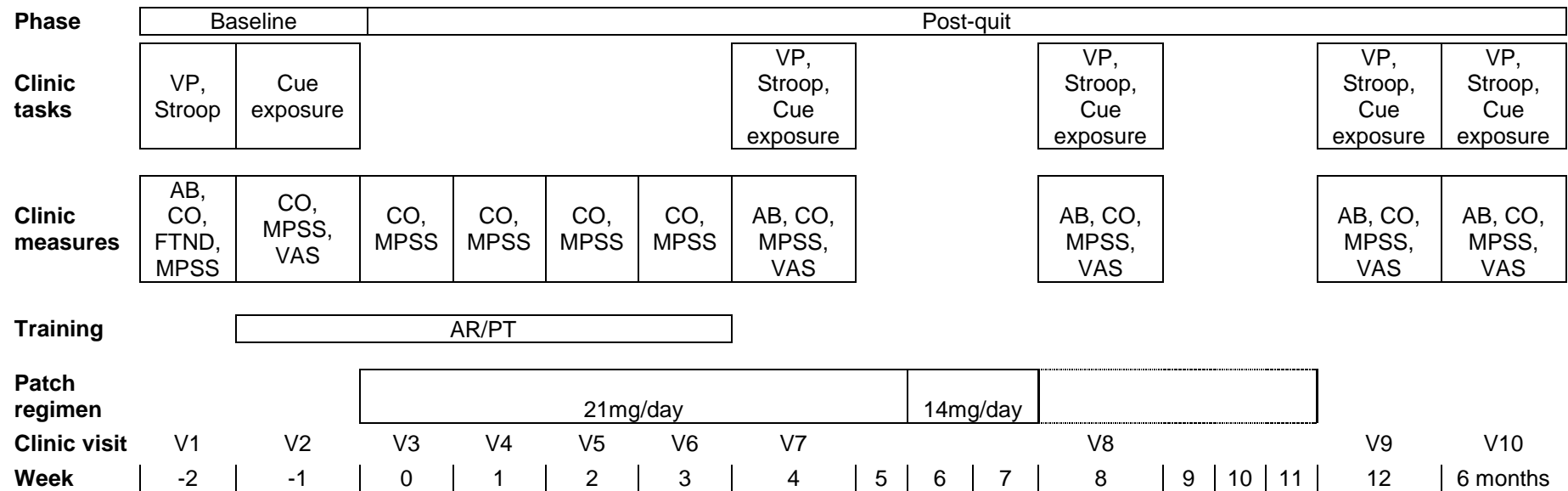
Written informed consent was obtained from all participants at the first session (Appendix 14), which took place two weeks prior to quit day. As there may have been circumstances in which participants wanted to delay their quit day, for example, owing to a family bereavement, participants were allowed to delay their quit attempt by a maximum of 14 days. Similarly, as it is not uncommon for people to miss their scheduled weekly appointments, participants were able to have their appointment rescheduled within 14 days of their last visit. Participants wishing to delay their quit attempt by more than 14 days or were unable to attend a rescheduled appointment within 14 days of their last visit were classified as abandoning their quit attempt and the participant was advised to contact their local stop smoking service at a time when they were ready to set a new quit date. Participants were provided with the name and number of their local stop smoking service.

### **3.2.6 Staff training**

Over the lifetime of the study, nine research nurses and three stop smoking advisors (SSAs) were trained to deliver the intervention. All staff completed a 2-day NHS stop smoking advisor course. They also attended a training day in which they were briefed on the clinical procedure on how to deliver each task (Appendix 15), and on use of the trial database. Prior to running a clinic, each member of staff observed a baseline session and week -1 (randomisation) session delivered by the chief investigator. In turn, the chief investigator observed the first two sessions delivered by each nurse/SSA involved in the study. Regular site visits were conducted to check that the intervention was being delivered as per protocol.

### **3.2.7 Trial Procedures**

Figure 14 provides an overview of the study procedures and clinic sessions. Participants in both trial arms were seen weekly in clinics from two weeks prior to quit day up to four weeks post quit day. There were ten clinic sessions in total. Randomisation took place at the second clinic session (see section 3.2.8) which initiated the first of the five weekly AR/PT sessions. Follow up visits took place at eight weeks and three months post quit day, with a final visit arranged at six months. Participants were reminded to attend their appointments by telephone or text message. Staff completed a case report form (CRF) at each clinic visit, which contained a checklist of the trial procedures (Appendix 16).



**Figure 14. Timeline of procedures and clinic visits. V=visit; VP=visual probe task; AR=attentional retraining; PT=placebo training; AB=attentional bias; CO=carbon monoxide; MPSS=Mood and Physical Symptoms Scale; VAS=visual analogue scale; mg=milligrams**



### 3.2.7.1 *Clinic measures*

At the first session, demographic and clinical characteristics of participants were collected using a baseline questionnaire (Appendix 17). Participant age, gender, ethnicity, education and employment status were classified using UK Census 2011 categories (Office for National Statistics, 2011). The questionnaire also contained information on smoking history including the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1991), a six-item measure assessing the severity of nicotine dependence.

Urge to smoke and withdrawal were measured at the beginning of every session using the Mood and Physical Symptoms Scale (MPSS). A modified version of the MPSS was used in which each of the nine items was rated on a scale from 1-7 (Appendix 18). Items relating to the strength and frequency of urges can be combined to produce a composite score (MPSS-C); this is also the case for combined mood items (MPSS-M). The MPSS was preferred over other measures such as the Questionnaire of Smoking Urges because of its superiority in predicting treatment outcomes (West, 2006; West & Ussher, 2010).

Exhaled carbon monoxide (CO) measurements were taken at the beginning of each session to biochemically verify smoking status. Attentional bias assessments were carried out using the visual probe task and pictorial Stroop task described in sections 3.2.7.3.1 and 3.2.7.3.2. Cue-induced craving was measured at the beginning of the second session and following attentional bias assessments (Appendix 19). The task is described in detail in section 3.2.7.3.3. A visual analogue scale (VAS) was used to measure craving on a 100

mm scale from “Not At All” to “Extremely” prior to and after the task. Lapses were recorded in the CRF at each clinic session. Knowledge on group allocation was measured in a questionnaire given at the end of the +4 week visit (Appendix 20). At eight weeks post-quit, acceptability of the training tasks was measured using a patient satisfaction questionnaire developed by the study team (Appendix 21).

### 3.2.7.2 *Materials*

Eighteen picture pairs of smoking-related and matched neutral pictures were used across attentional bias assessment and training tasks (picture pairs 1-18). These stimuli have been tested and applied in previous research (McClernon et al., 2007; McClernon et al., 2008). Each set of pictures consisted of a colour photograph of a smoking-related stimulus or scene (e.g. a close-up of a cigarette) matched on age, sex, complexity and ethnicity to another photograph containing no smoking-related content (example provided in Appendix 22). In the assessment version of the visual probe task and pictorial Stroop task, twelve picture pairs were used (picture pairs 1-12). Similarly in the AR and PT versions of the visual probe task, the twelve picture pairs consisted of six picture pairs featured in the assessment version of the task (picture pairs 7-12) in addition to six new picture pairs (picture pairs 13-18). An extra four neutral picture pairs were used for practice trials before each task.

### 3.2.7.3 *Clinic Tasks*

#### 3.2.7.3.1 *Visual probe task*

At the baseline session and again at four weeks post-quit, eight weeks, three months and six months, all participants completed the assessment version of the visual probe task. The assessment version, which was used to measure attentional bias, comprised a total of 192 trials, presented in two blocks. Each trial began with a fixation cross displayed in the centre of the computer screen for 500 ms. A picture pair of smoking-related and neutral pictures was then presented side-by-side on the screen for 500 ms. After this picture pair disappeared, a visual probe was presented in the location formerly occupied by one of the pictures. This probe was either a circle (●) or square (■). Participants were required to discriminate the identity of the probe and respond accordingly by pressing the up or down arrow keys on the keyboard as quickly as possible. There was a 500 ms interval before the next trial. Presentation of each picture-pair and probe location was counterbalanced. In all trials, the visual probe replaced the smoking-related and neutral pictures with equal frequency. At the start of the task, participants carried out eight practice trials in which neutral picture pairs were presented first, to allow them to become familiar with the procedure.

Each block of trials were presented in a new random order for each participant, using EPrime version 2 (Psychology Software Tools Inc., Pittsburgh PA). The task took approximately 16 minutes to complete. Attentional bias scores were calculated from reaction time (RT) data; an attentional bias towards smoking cues was characterized by faster reaction times towards smoking-related pictures than neutral pictures.

#### 3.2.7.3.2 *Pictorial Stroop task*

All participants carried out a pictorial Stroop task as an additional measure of cognitive bias. The pictorial Stroop task was given after the visual probe task at the baseline session and again at four weeks post-quit, eight weeks, three months and six months. The task comprised a total of 192 trials, presented in four blocks of 48 trials, with each block consisting of smoking-related pictures or neutral pictures only. Each picture was presented centrally on a computer screen, with either an outline of a red, blue, yellow or green border. Participants were required to indicate the colour of the border, while ignoring the picture, by pressing one of four corresponding labelled keys on the keyboard, as quickly as possible. Participants received eight practice trials in which neutral pictures were presented first, to allow them to become familiar with the procedure. A short break between blocks was permitted.

Each block of trials was presented in a new random order for each participant, using EPrime version 2 (Psychology Software Tools Inc., Pittsburgh PA). The task took approximately 12 minutes to complete. Stroop bias scores were calculated from RT data; selective processing towards smoking cues was characterized by slower reaction times towards smoking-related pictures than neutral pictures.

#### 3.2.7.3.3 *Cue exposure task*

At one week prior to quit day, four weeks post-quit and follow-up sessions at eight weeks, three months and six months, participants in both groups were given a cue exposure procedure to measure cue-induced craving immediately after completion of the visual

probe task and pictorial Stroop task. This is a common procedure in cue-reactivity research (Sayette & Hufford, 1994; Shiffman et al., 2003). Showing a strong craving response to cue-exposure has been shown to predict relapse risk (Abrams et al., 1988). Prior to attending the session at week -1, participants were instructed to abstain from smoking for at least one hour. We chose an abstinence period of one hour to avoid floor effects in craving ratings, commonly found immediately after smoking (Schuh & Stitzer, 1995).

In order to standardize the procedure, instructions for the cue exposure task were recorded on a digital recorder, which was then played to participants in the relevant clinic sessions. Before the instructions were played, participants provided a single rating of their urge to smoke on the VAS. The therapist placed a box that concealed a cigarette and a lighter in front of the participant. The recording was then played, which instructed the participant to lift up the box and handle the cigarette and lighter contained within. The task lasted three minutes. Following the task, participants provided another rating of their urge to smoke on the VAS.

#### *3.2.7.4 Reimbursement to participants*

Participants were paid £15 to complete assessments at the three month and six month follow-up sessions, as these were not therapeutic encounters.

### **3.2.8 Randomisation**

Participants were randomised 1:1 to either AR or PT using a computer generated simple randomisation scheme, ordered in random permuted blocks of four. The sequence were generated by the trial statistician and entered on to a dedicated online trial database by an independent programmer in the Primary Care Clinical Research and Trials Unit (PCCRTU) at the University of Birmingham. At one week prior to quit day, at the start of the clinic session, the therapist accessed the randomisation section of the trial database and clicked on a button that revealed a letter ('A' or 'B') to reveal the training task to which the participant was allocated. The training tasks were contained within two folders labelled 'Training A' or 'Training B' on the study laptop, which concealed whether the procedure was AR or PT. These folders were labelled by an independent researcher prior to the start of the trial. Thus the participants, therapists and study staff were blinded to allocation, to minimize the risk of bias.

### **3.2.9 Treatments**

#### **3.2.9.1 Control group**

Participants allocated to the control group carried out five weekly sessions of PT, starting one week prior to their designated quit day. During each session, participants carried out eight practice trials of neutral picture pairs followed by 192 trials of PT, presented in two blocks. Between each block, participants were permitted to have a short break if required. The task took approximately 16 minutes to complete. On each PT trial, the visual probes always replaced smoking-related and neutral pictures with equal frequency.

### *3.2.9.2 Intervention group*

Participants allocated to the intervention group carried out five weekly sessions of the modified visual probe task, AR, starting one week prior to their designated quit day. Eight practice trials of neutral picture pairs were presented prior to the first block of AR trials. A total of 192 training trials were presented in two blocks, where participants had the opportunity to have a break in between. The task took approximately 16 minutes to complete.

The AR program differed from the PT program only in the location of the visual probes. During each training trial, visual probes always appeared in the location of the neutral pictures. Thus, participants always had their attention directed away from smoking-related pictures.

### *3.2.9.3 NHS stop smoking support*

Systematic reviews have shown that some behavioural and pharmacological interventions increase people's chances of successfully stopping smoking (Stead et al., 2008; Lancaster & Stead, 2005). All participants were therefore given NRT in the form of transdermal nicotine patches and received standard withdrawal orientated behavioural support (Hajek, 1989).

#### *3.2.9.3.1 Trial Medication*

Participants in this trial were offered 21mg/24 hour nicotine patches as the only choice of treatment. This was because:

- 1) All participants were regular smokers for whom the 21mg dose was deemed appropriate.
- 2) The study aimed to examine the effects of attentional retraining on urge to smoke. Short-acting NRT e.g. inhalator or gum affect cue-induced urges to smoke and reduce their intensity (Ferguson & Shiffman, 2009). It would have thus been difficult to assess the effects of the attentional retraining if short-acting NRT was used. Participants were also not permitted to use varenicline for the same reason (Aubin et al., 2008). Investigators have found that nicotine patches do not protect against cued craving (Waters et al., 2004), therefore we considered that patch-use was unlikely to mask the potential effects of retraining.
- 3) The patch is the best tolerated form of NRT and has the highest adherence (Hajek et al., 1999; Jorenby et al., 1995).

#### *3.2.9.3.2 Dose alteration procedure*

Nicotine patches are well tolerated in the large majority of regular smokers and so we expected that most people would continue with the standard dose. However, there are circumstances when the form or dose of the preparation needs to be changed. This variation reflects pragmatic behaviour in the NHS stop smoking services and was expected to be equal in both arms. We anticipated the following occurrences:



- 1) Minor skin irritation to the patch is one of the most common problems with use. This is commonly eased by swapping from one form of patch to another, because it is usually intolerance to the glue. If the skin reaction was worse, such as causing blisters that could not be remedied by emollients and hydrocortisone cream, patch use was stopped and the participant was swapped to an equivalent dose of oral NRT.
- 2) Sleep disturbance or vivid dreaming is also one of the most common problems with use of the nicotine patch. This can usually be eased by removing the nicotine patch an hour or so before bedtime and so this was advised. There is no good evidence that 16 hour patch use is less effective than 24 hour patch use.
- 3) Possible symptoms that dose is too high are uncommon problems, but possible. Nausea is the earliest symptom of overdose, but it is also a common symptom experienced by people often enough. Nicotine has a short half life, meaning that by about 10 hours after first applying a patch, nicotine has reached a steady state. Therefore nausea occurring for the first time days after starting treatment is unlikely to be due to the patch. More definite symptoms are as follows, muscular twitching, dizziness, confusion, rapid pounding heart, high blood pressure, vomiting, and weakness. However, 21mg/24 hour patch systems come as 14mg/24 hours and 7mg/24 hours, which can be used in a step down system. If the therapist thought that an overdose was likely, the precaution taken was to step down the dose to the next step i.e. from 21mg to 14mg, or from 14mg to 7mg.

#### *3.2.9.3.3 Duration of treatment and instructions for use*

Treatment with NRT started either on the evening prior to quit day or the morning of quit day, depending on personal preference. Patches were dispensed accordingly during the second visit, which was one week prior to quit day. Instructions for patch use included changing it every 24 hours, using a different area of skin for the new patch. Participants were advised to continue using the patch for at least eight weeks or stop if they abandoned their quit attempt before the 8 weeks. The therapist in consultation with the patient may have chosen to step down the patch as discussed above. Step down was not necessary as there is no evidence to suggest that it enhances efficacy, but it is commonly perceived as helpful by patients. Step down towards the end of treatment was not permitted to commence until at least four weeks after quit day. The therapist was instructed not to suggest stepping down in people who had recent lapses. Some PCTs that were involved in the trial did not allow treatment for longer than 8 weeks, but, in those that did, the therapist consulted the participant about longer courses of treatment up to 12 weeks duration. This decision was at the discretion of the therapist in consultation with the patient.

Behavioural support started two weeks prior to quit day, and lasted up to four weeks after quit day. This followed the typical 7-session withdrawal orientated therapy programme offered in existing NHS stop smoking services (Hajek, 1989).

#### *3.2.9.3.4 Reporting of adverse events*

This was not a trial of an investigational medical product. Indeed we used a licensed medical product within the terms of its license and in accord with clinical guidelines. We therefore expected relatively few problems and so no special reporting requirements were made. The therapist leading the sessions managed problems within his/her own competence. Clinical advice was sought from the trial doctor. Between them, the therapist and trial doctor decided how to manage unexpected problems and whether to report a suspected unexpected serious adverse reaction (SUSAR) to the Medicines and Health Care Regulatory Authority using the yellow card system (this is a standard system for reporting unusual reactions to medication).

However, for the purposes of the trial, we recorded clinically significant adverse events that led to a change in medication management or was otherwise so significant that it was odd not to record them. This allowed us to track changes in medication instruction, such as swapping to 16 hour use or dose alterations. The CRF was used to record the date, the nature of the adverse event/symptoms, and the action taken (Appendix 16).

### **3.3 Trial Outcomes**

#### *3.3.1 Primary trial outcomes*

- Measure of attentional bias during assessment trials of the visual probe task, as measured by the difference in median reaction time taken (in ms) to respond to probes replacing smoking-related stimuli versus probes replacing neutral stimuli.

This was assessed at four weeks post-quit in abstinent and non-abstinent smokers across both trial arms, following recommendations of Shiffman et al. (2004b).

- Strength of weekly urge to smoke on the MPSS, measured up to four weeks post-quit in abstinent and non-abstinent smokers across both trial arms.

### **3.3.2 *Secondary trial outcomes***

- Strength of withdrawal symptoms on the MPSS, measured up to four weeks post-quit in abstinent and non-abstinent smokers across both trial arms.
- Prolonged abstinence measured and biochemically validated at four weeks post-quit and each follow-up using the Russell standard (West et al., 2005). Criteria for the Russell standard includes a two week grace period from quit day, followed by smoking no more than five cigarettes and verification by means of exhaled CO, with a cut-off point of <10ppm.
- Time to first lapse, with a lapse episode defined here as any smoking, even a puff (West et al., 2005).

### **3.3.3 *Other trial outcomes***

- Feasibility of running the ARTS trial within NHS SSS assessed on the basis of:
  - Rates of response to patient invitation letters;
  - Rates of recruitment at telephone screening;
  - Rates of attendance at clinic sessions;
  - Rates of drop out prior to and after randomisation.

- User acceptability as measured by ratings of perceived usefulness on a patient satisfaction questionnaire.
- Change in cue-induced cravings measured on the VAS prior to and at the end of the cue-exposure task at four weeks, eight weeks, three months and six months post-quit day in abstinent and non-abstinent smokers across both trial arms.
- Measure of cognitive processing bias on the pictorial Stroop task, to assess generalization of attentional retraining effects at four weeks post-quit in abstinent and non-abstinent smokers across both trial arms. Stroop bias was measured by the difference in median reaction time taken to respond to colour-naming of smoking-related stimuli versus colour-naming of neutral stimuli.
- Measure of attentional bias towards novel untrained stimuli on the visual probe task at four weeks post-quit in abstinent and non-abstinent smokers across both trial arms.
- Measure of attentional bias on the visual probe task and pictorial Stroop task at eight weeks, three months and six months to assess long term effects of attentional retraining.
- Strength of urge to smoke and withdrawal symptoms on the MPSS, measured up to eight weeks, three months and six months to assess long term effects of attentional retraining.

### **3.4 Observational Study Outcomes**

- Association between attentional bias and nicotine dependence
- Association between attentional bias and urges to smoke
- Association between attentional bias and withdrawal symptoms

- Association between attentional bias and smoking abstinence

### **3.5 Trial Statistics**

The sample size was based on the following calculations. In these calculations, we assumed that only quitters would continue to attend clinic and that the measures were analysed only in abstinent smokers, as is standard practice with withdrawal phenomena (Shiffman et al., 2004b).

We assumed that the effect of five sessions of attentional retraining would be no greater than the effect of a single session. From the findings of the Attwood et al. (2008) study, to detect a mean reduction of 26 ms (SD=43 ms) with 80% power and a type 1 error rate of 5%, 42 participants in each group were required. We revised this calculation to adjust for baseline attentional bias scores. In our laboratory study of AR (Chapter 2), we found an estimated correlation coefficient of -0.13 between baseline and post-training measurements. Thus, to detect a reduction of 26 ms with the same standard deviation, power and type 1 error stated above, 42 participants were still required in each group. We expected that at least 50% of participants would reach the Russell standard abstinence criteria at 4 weeks, as the NHS services achieve greater than this, providing about 50 abstinent participants in each arm, sufficient to test this hypothesis.

The trial was an exploratory study but was powered to detect differences in urge to smoke. One study on smokers quitting on pharmacotherapy found that the mean change in urge strength between quit day and week one was about 0.5 points measured with the

MPSS and had a SD of 1.2 (Aveyard et al., 2008). Another study reported that glucose reduced urge strength by 1.0 points, although this was immediately after dosing (West et al., 1999). In both of these studies, MPSS urge strength was scored from zero to five (West & Hajek, 2004). We assumed that if AR could reduce urge strength by 0.6 points, then 62 participants in each group would have been needed to detect this with 80% power and a type 1 error rate of 5%. From the earlier study (Aveyard et al., 2008) we used an estimated correlation coefficient of 0.41 between quit day and post-training urge strength to adjust this power calculation. This meant that to detect a 0.6 point reduction in urge strength (SD=1.2) with 80% power and a type 1 error rate of 5%, 53 participants would be required in each group. In the first four weeks, when withdrawal is at its height, this implied that about 200 smokers were needed, assuming that 60% would achieve abstinence in the first four weeks.

### ***3.5.1 Loss to follow-up***

Participants who failed to attend clinic and did not respond to our telephone calls were classed as smokers for the analysis of smoking abstinence, as is standard (West et al., 2005). We had expected to make contact with more than 90% of people at the six month follow-up, based on experiences of a recent trial (Aveyard et al., 2008). We anticipated that the effects of attentional retraining on attentional bias and withdrawal phenomena would be analysed primarily in abstinent smokers, as recommended by Shiffman et al. (2004b), so defaulting from routine clinic appointments by failed quitters was not considered a threat on the integrity of the trial. We therefore did not require those participants who failed to maintain abstinence and abandoned their quit to continue to attend clinics except for reasons detailed below.

We considered that this study could give valuable information on what happens to attentional bias over time, how it is affected by training, how it is affected by resuming smoking, and whether the training effect is contingent on continued abstinence.

Accordingly, we asked all participants regardless of smoking status to attend the follow-up sessions and compensation was provided to increase the likelihood of attendance (section 3.2.7.4).

## **3.6 Regulatory Procedures**

### ***3.6.1 Definition of end of trial***

End of trial was defined as the final six month follow-up assessment of the last participant undergoing the trial.

### ***3.6.2 Monitoring and audit***

The progress of the trial was monitored by quarterly review of records. We checked that consent information was available for all participants and that the inclusion and exclusion criteria were being adhered to. Data cleaning took place by a series of checks on the trial database, for example, a participant could not be recorded as a prolonged abstinent smoker at eight weeks if they had not been recorded abstinent at four weeks.

Discrepancies on the trial database were checked with the source documents (e.g. CRFs and data stored on the study laptops) and amended where necessary.



### **3.6.3 *Data management***

The trial was conducted as part of the portfolio of trials in the Primary Care Clinical Research and Trials Unit (PCCRTU), a National Institute for Health Research (NIHR) recognised trials unit in Primary Care Clinical Sciences at the University of Birmingham. The data management followed standard operating procedures, which were fully compliant with the Data Protection Act and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The source documents for the trial were stored in the trials unit, in a locked cabinet, in a locked office. The PCCRTU maintained the trial database.

Upon completion of the trial and analyses of all data, we transferred the source documents to a secure archiving facility at the University of Birmingham. Here, they will be held for 15 years and then destroyed. The PCCRTU anonymised the trial database.

### **3.6.4 *Data protection and confidentiality***

Data were kept in accordance with the Data Protection Act. The trial was registered with the Data Protection Act website at the University of Birmingham. As mentioned in section 3.6.3, the standard operating procedures of the trials unit were followed, which were designed to protect patient confidentiality. Patient identifiable data were shared only within the immediate study team on a need-to-know basis. This was to ensure the provision of adequate clinical care and appropriate follow-up. Participants gave consent for their data to be shared with their general practitioner, or approved auditors from the

Research Ethics Committee or NHS Research and Development, where necessary. No one outside of the study team had access to the source documents or the trial database.

### **3.6.5 *Ethics and Research Governance***

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the ICH-GCP, the EU Clinical Trials Directive and all applicable regulatory requirements. The study protocol and other documentation were approved by the National Research Ethics Committee (10/H1206/34) and local NHS Research & Development offices. Subsequent protocol amendments were submitted to the Research Ethics Committee for approval, and the other bodies where necessary. We provided the Research Ethics Committee with annual progress reports, in addition to a final study report.

## **3.7 Funding**

The study was funded by the National Institute for Health Research (NIHR). Service support costs were claimed via the Comprehensive Clinical Research Network. Treatment costs were covered by the NHS SSS.

## **CHAPTER 4: ASSESSING THE FEASIBILITY AND ACCEPTABILITY OF ATTENTIONAL RETRAINING IN PRACTICE –FINDINGS FROM THE ARTS TRIAL**

### **4.1 Introduction**

As described in Chapter 3, our first objective of the ARTS trial was to explore the feasibility of delivering the AR intervention within NHS stop smoking clinics and assess the acceptability of AR procedures to NHS patients. No study has yet investigated the use of computerized interventions like these in practitioner-led NHS stop smoking clinics. Chapter 4 therefore describes how we assessed the feasibility of the intervention by examining the study processes and outcomes that include: the rates of response to patient invitation letters, recruitment at telephone screening, attendance at clinic sessions and rates of drop out prior to and after randomisation. Acceptability of the trial procedures was assessed further by adherence to the tasks and patient satisfaction.

### **4.2 Study processes**

#### ***4.2.1 NHS regulatory approvals***

There were delays in obtaining NHS permissions to run the trial. We initially applied for NHS permission to run the trial in seven Primary Care Trusts (PCTs): Birmingham East and North (BEN), Heart of Birmingham (HoB), South Birmingham (SB), Dudley, Sandwell, Warwickshire and Worcestershire PCTs.

Although all applications were submitted concurrently in March 2010, ethical approval was granted from Birmingham East, North and Solihull Research Ethics Committee in May 2010 (REC reference number 10/H12006/34), while R&D approvals for BEN, HoB, SB and Sandwell PCTs were obtained in August 2010 (Appendix 23). Honorary contracts that allowed research staff to access NHS premises were issued in October/November 2010; research activity could only commence at these sites from this point forward.

We did not gain approval to run the trial in Dudley PCT because two other smoking cessation trials were already operating within the Trust and they would not fund the NRT treatment costs. Similarly, Warwickshire PCT did not agree to fund the excess treatment costs. At the time of applying for permissions, Worcestershire PCT were undergoing a major change to the delivery of their stop smoking services and for this reason, did not take on the trial.

We later sought further ethical approval to run the trial from additional sites including Walsall Teaching (Wt) PCT and community venues within Birmingham Community Healthcare Trust (BCHCT) in an attempt to improve our recruitment rates (see section 4.2.3.1.2).

#### **4.2.2 *Stage 1 recruitment strategy***

We initially identified and recruited GP practices within BEN, HoB and Sandwell PCTs; the study was later rolled out in Wt PCT.

Each practice identified potential participants through electronic searches of their patient databases. Search criteria included patients who were registered as current smokers and over the age of 18. The practice staff checked the patient lists for any exclusions prior to invitation letters being sent out (e.g. if a patient was deceased). Letters were typically sent in batches of 200, based on response rates to the previous mail shot. Referrals were also sought from the GPs, who gave contact details of our research team to potential participants during consultations.

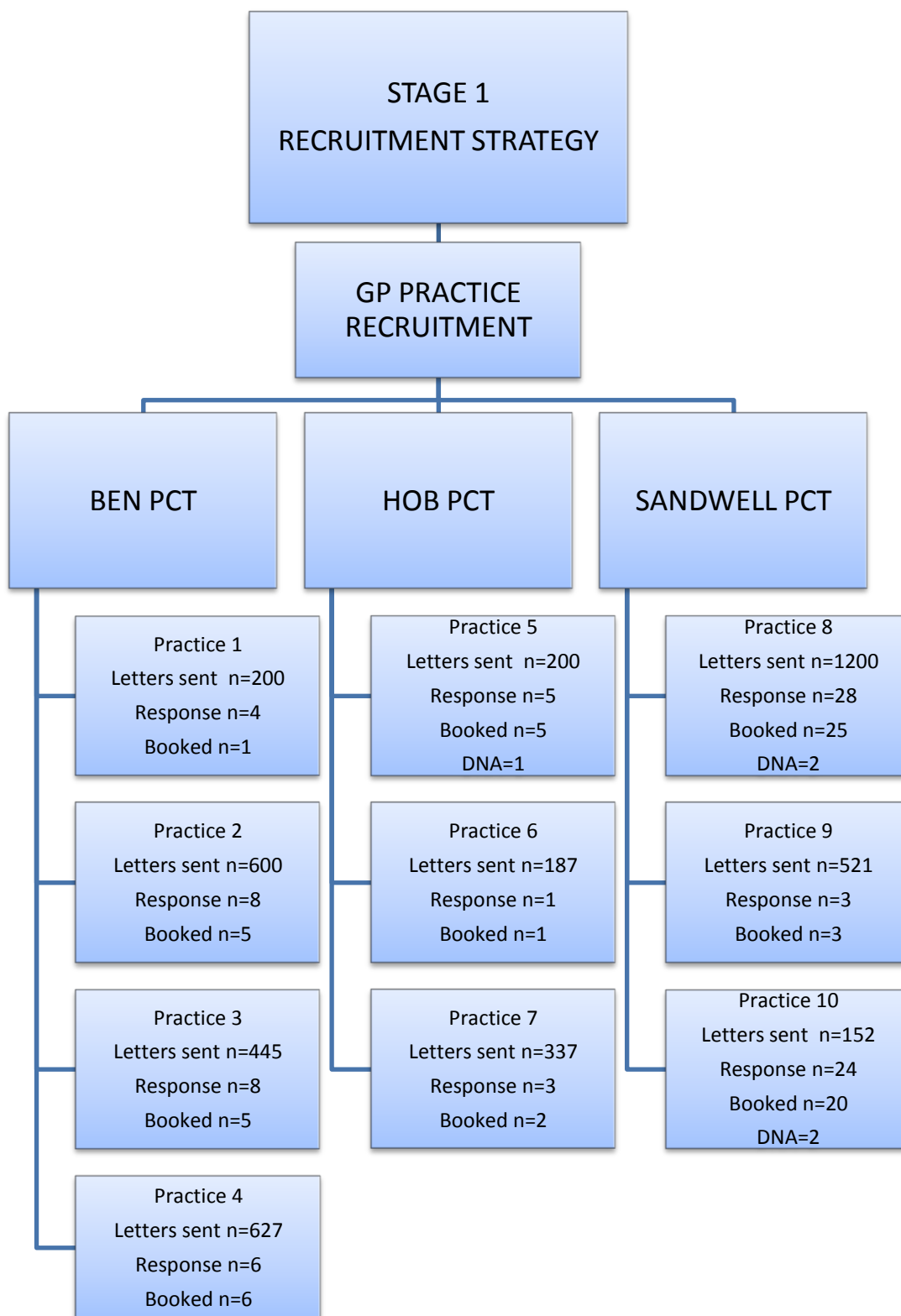
#### *4.2.2.1 Outcome of stage 1 recruitment strategy*

##### *4.2.2.1.1 Response and recruitment rates by PCT*

Figure 15 shows response and recruitment rates to the stage 1 recruitment strategy. In BEN PCT, four GP practices identified a total of 3598 smokers from their patient database searches; 1872 letters were sent out to potential participants of which 26 (1.4%) contacted the research office and were screened for eligibility. Of these respondents, 17 (1.0%) were booked for a baseline session and were enrolled in the study.

In HoB tPCT, three practices identified 723 smokers from their patient searches and sent invitation letters to all potential participants, of which 9 (1.2%) responded and 8 (1.1%) were booked for a baseline session.

Three practices in Sandwell PCT identified and sent invitation letters to a total of 1873 smokers on their patient databases; 55 (2.9%) potential participants responded and were screened for eligibility, of which 48 (2.6%) were booked for a baseline session.



**Figure 15. Response and recruitment flow by PCT and practice during stage 1 recruitment**

#### 4.2.2.2 *Challenges of stage 1 recruitment strategy*

Although an additional two practices in HoB tPCT expressed an interest in the study, we did not pursue patient recruitment any further at this site for three reasons. Firstly, given the poor response rate from the existing three practices - which was considerably less than the 5-10% estimated – it was clear that we would not meet the desired recruitment rate of 3/4 patients per week to reach the target sample size within our timescale. Secondly, our resources were limited; the additional cost and time associated with setting up these practices as well as the lack of staff availability outweighed the likelihood of recruiting an adequate number of participants from these practices to make this approach worthwhile. Thirdly, HoB tPCT covers an area of Birmingham with a diverse, ‘hard-to-reach’ population. Other smoking cessation studies have reported difficulties with recruitment from practices within HoB tPCT because of its demographic profile. After discussing the trial with the practice staff at these two practices, concerns were raised as to whether their patients would understand the trial procedures and stop smoking programme, as at least 70% were of Black or Asian ethnicity, and English was not the first spoken language for the majority. All trial materials were written in English and none of our staff could speak the languages required (e.g. Punjabi, Urdu, Gujarati). For these reasons, we deemed it impractical to recruit further from HoB tPCT and there were no other practices that could be approached in BEN PCT. This led to the decision to begin practice recruitment in Sandwell PCT.

Despite an improved response rate in Sandwell PCT compared to BEN PCT and HoB tPCT, we had exhausted the list of potential practices we could approach and thus our recruitment strategy required revision.



We had NHS regulatory approval to deliver in SB PCT; however we did not recruit practices at this site for two reasons. Firstly, we considered that participant recruitment may have reached saturation in the practices within this area as many practices had recently taken part in other smoking cessation trials using the same recruitment strategy. Another reason was that several practices had signed up to a Local Enhanced Service (LES) scheme in which they had their own in-house stop smoking service and were paid for service provision; the tobacco-control lead at SB PCT did not want the study to be carried out at these practices as it was thought that doing so would complicate the way that payments were made for patients seen by our study team.

#### ***4.2.3 Stage 2 recruitment strategies***

In light of the poor response rate from our approved sites and the restrictions posed on practice recruitment in SB PCT, we implemented a number of changes in an attempt to increase our recruitment rate including:

- a) Increasing the number of sites
- b) Targeting a new population group
- c) Increasing reach of study via new advertising methods

Substantial amendments were submitted to the Birmingham East, North and Solihull Research Ethics Committee in order to proceed with these changes and approvals were received.

### *4.2.3.1 Changes to recruitment approach*

#### *4.2.3.1.1 Increasing the number of sites*

We had exhausted practice recruitment in our existing sites; it was therefore necessary to recruit from a) different venues and b) a different geographical area that other smoking cessation studies had not recently operated in.

While we were unable to recruit any practices in SB PCT, we attempted to recruit from within the community by holding a clinic at the University of Birmingham. As this was classed as a community venue, we obtained approval to carry out the study within BCHCT. The clinic was advertised locally, on the University website, in staff newsletters, staff payslips, the University magazine and later through social media (see section 4.2.3.1.3).

From April 2010, eight PCTs in the West Midlands opted into a new tariff-based scheme in which organisations were commissioned by the PCT to provide stop smoking services via a payment on results contract (Department of Health, 2011). We identified Wt PCT – which was part of the consortium that opted into the scheme - as a potential area for recruitment. We gained NHS regulatory approvals for this additional site, but were unable to start recruitment unless our organisation (the University of Birmingham) became a registered provider of stop smoking services. The application to become a stop smoking service provider was accepted in January 2012.

#### *4.2.3.1.2 Targeting a new population group*

We approached BCHCT in order to target smokers who had a history of failed quit attempts. The SSS at BCHCT searched all residents of South Birmingham, over the age of 18, who had accessed the stop smoking services from April 2010 - April 2012 and were classed as non-abstinent at four weeks post-quit.

We increased the flexibility of our clinics beyond the normal weekday working hours to include weekend clinics and appointment times after 7pm on weekdays. We also secured another community venue to increase access to the services, in addition to offering the University as the main venue for clinics.

#### *4.2.3.1.3 Increasing reach of study via new advertising methods*

We initially advertised the University clinic to staff and students of the university through posters and leaflets (Appendix 24). To boost the number of recruits into the clinic, we advertised more widely through an online social media campaign via the website Facebook (Appendix 25). The advert was publicised to people living within a 16 kilometre radius of Birmingham, and was released from 22/03/2012 - 01/04/2012 and 20/06/2012 - 09/07/2012. The cost we incurred depended on the number of times the advert was viewed, with each viewing capped at a charge of £0.59.

#### *4.2.3.2 Outcome of stage 2 recruitment strategy*

Figure 16 shows response and recruitment rates to the stage 2 recruitment strategy.

#### *4.2.3.2.1 Response and recruitment rates according to the increase in the number of sites*

From August 2011 – March 2012, the University clinic yielded 42 respondents of which 37 participants were booked in for a baseline session. This equated to a monthly average of five respondents, out of which four people were booked in for a baseline session per month.

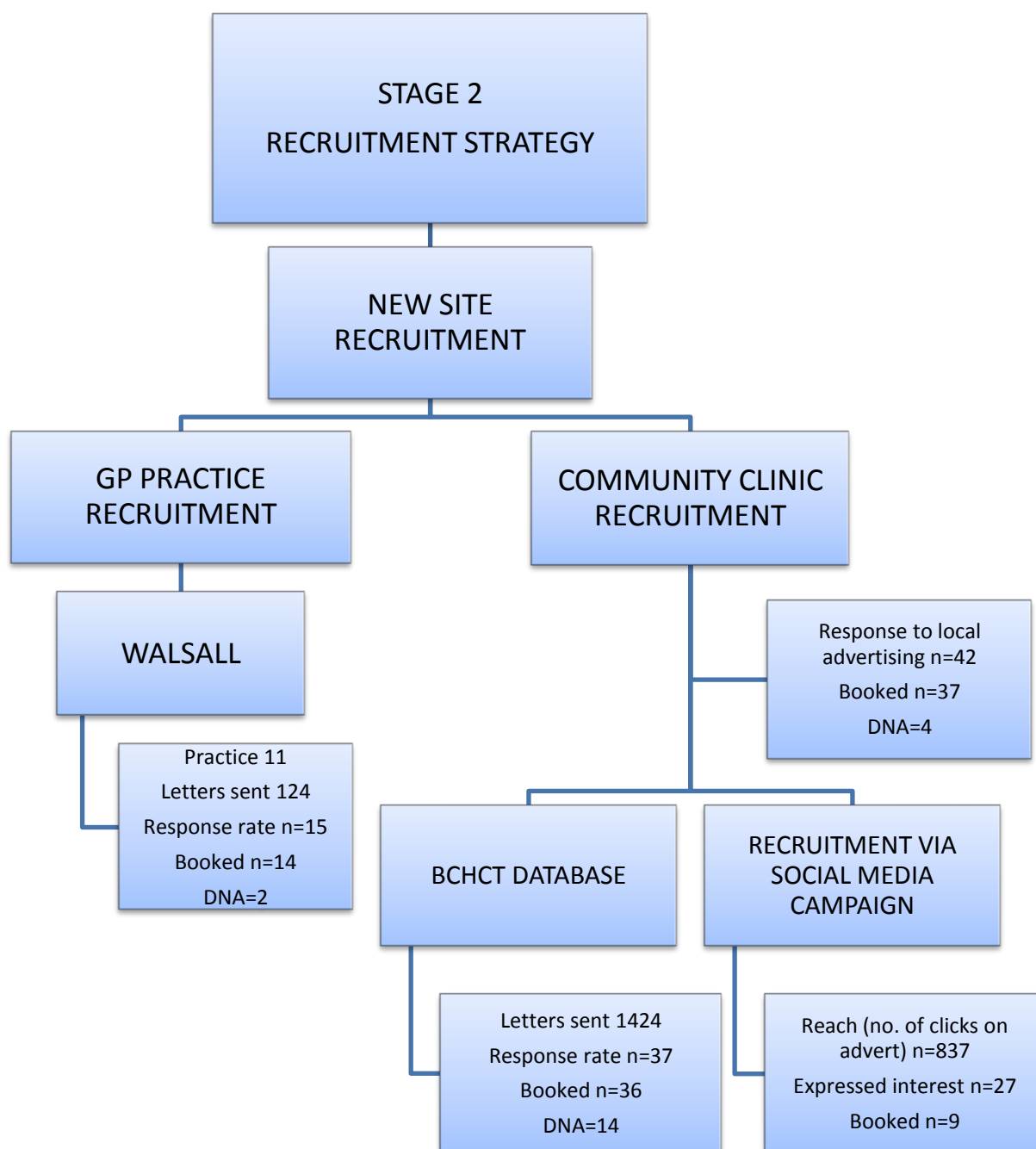
One practice in Walsall identified and sent invitation letters to 1204 smokers, of which 15 (1.2%) were screened for eligibility and 14 (1.2%) were booked for a baseline session.

#### *4.2.3.2.2 Response and recruitment rates according to new population targeted*

A total of 1424 smokers were identified and sent invitation letters to take part in the study from the BCHCT database, of which 37 (2.6%) contacted the research office and 36 (2.5%) were booked in for a baseline session.

#### *4.2.3.2.3 Response and recruitment rates according to online social media campaign*

The advert was clicked on 837 times, of which 27 (3.2%) expressed an interest in the study, 12 (1.4%) of whom left contact details and were screened for eligibility and 9 (1.1%) booked for a baseline session. Over the lifetime of the advert, an average of three people per week were booked in for a baseline session. The total cost of advertising was £490.31.



**Figure 16. Response and recruitment flow by site during stage 2 recruitment**

#### 4.2.3.3 *Challenges of stage 2 recruitment strategy*

Recruiting from the University of Birmingham provided a steady stream of participants into the study, but did not allow us to recruit quickly enough to catch up with our forecasted recruitment rate.

Carrying out the study in a tariff area meant that our organisation was in competition with other providers who were also seeking to provide their services to GP practices, many of whom were already operating within several practices. As a result, we only gained access to one practice in Wt PCT within our timescale.

Of the 27 respondents that expressed an interest in the study from the Facebook advertisement, a large proportion did not leave their contact details (55.6%). Arguably, non-smokers as well as smokers could have clicked on the advert, meaning that the response rate could be somewhat higher than stated if only those who were interested in stopping smoking were used in this calculation. While it may seem counterintuitive that non-smokers clicked on the advert (as this would have led to an increase in advertising costs) we cannot rule out that they could have passed on the study details to smokers who were interested in quitting. The advantage of the campaign was that it could reach a large number of people within a short timeframe, so much so that this strategy enabled us to meet the anticipated recruitment rate of 3/4 people per week. Despite this improvement, we did not have the resources to continue this method of recruitment.

#### **4.2.4 Participant flow**

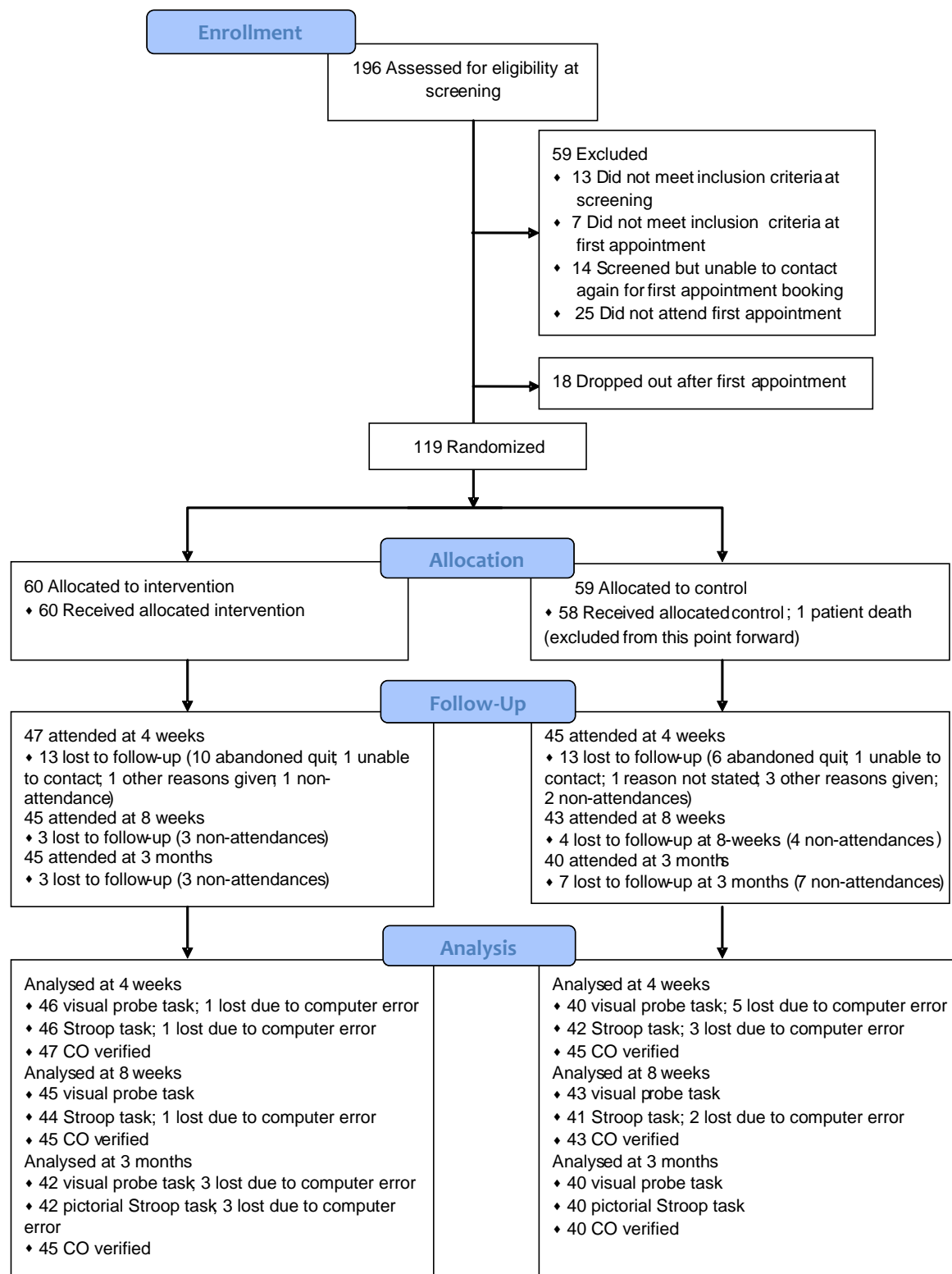
The recruitment period spanned from April 2011 and October 2012; recruitment was stopped before reaching the target sample size of 200, due to lack of resources and time constraints. Figure 17 depicts the flow of participants through the trial. Of the 196 assessed for eligibility, 137 attended a baseline session and 119 went on to be randomised at the second session.

##### *4.2.4.1 Attrition rates*

Eighteen (13.1%) participants dropped out of the study prior to randomisation, the majority of whom said this was because they had abandoned their quit attempt (33.3%). Of the 119 participants that were randomised, 23 (19.3%) dropped out of treatment and subsequent follow-up visits after randomisation. The most commonly cited reason for drop out was that participants had abandoned their quit attempt (69.6%). There was no difference in the risk of drop out between groups (RR=0.99, 95% CI=0.83, 1.19, p=0.89).

##### *4.2.4.2 Attendance rates*

The median number of clinic visits attended by all participants was 8 out of a possible 9 visits; there was no difference between trial arms ( $t[116]=0.12$ ,  $p=0.91$ ). The median number of training sessions attended was 4.5, which was the same across both groups ( $t[116]=0.24$ ,  $p=0.81$ ).



**Figure 17. Flow of participants through the trial**

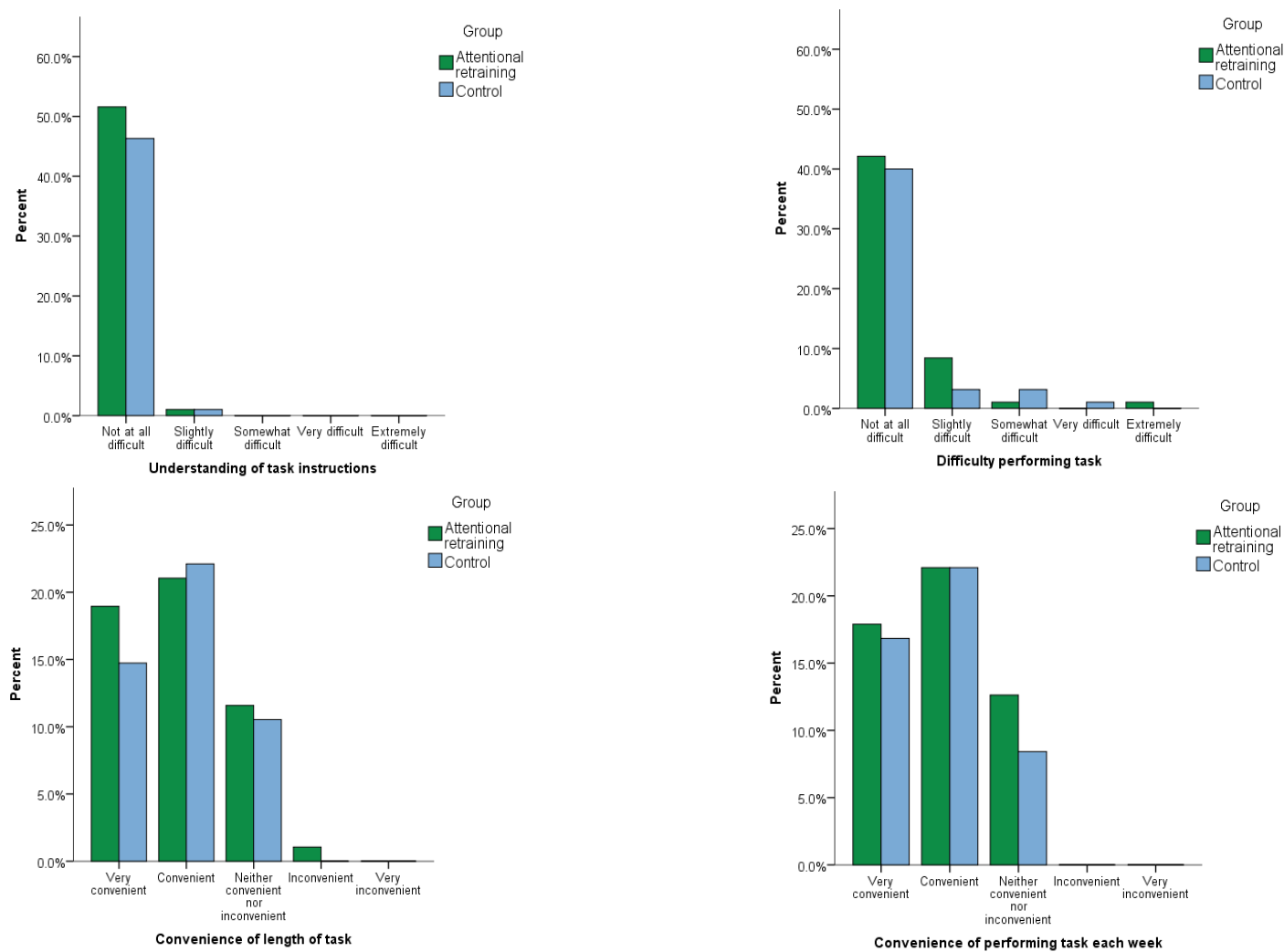


### **4.3 Acceptability of ARTS intervention to patients**

Acceptability of the training procedure was assessed by a patient satisfaction questionnaire given to all participants at the eight week post-quit follow up visit (Appendix 21). Two items related to how difficult the task was to understand and carry out, while a further two items assessed the convenience of task. Items were rated on a 5-point scale ranging from “not at all difficult” to “extremely difficult” and “very convenient” to “very inconvenient”. Adverse events were recorded by stop smoking advisors at each clinic visit.

#### ***4.3.1 Patient satisfaction***

Of the 118 participants who were randomised (one participant excluded from subsequent analyses due to death), 95 (80.5%) responded to the patient satisfaction questionnaire (Figure 18). Most participants did not find the task instructions difficult to understand or difficult to carry out. Most found the length of the task convenient or expressed indifference; similarly the majority found the task convenient to carry out each week. Overall, approximately half (51.7%) of respondents said that they would use attentional retraining if it helped them stop smoking; 22.9% responded that they would use the task but had some reservations; 3.4% said that they would use the task but had a lot of reservations and 2.5% said they would not use the procedure at all. The most common reasons stated among the 34 participants who said that they would not use the task or had reservations in using it included boredom (23.5%) and the task being too long (20.6%).



**Figure 18. Patient satisfaction questionnaire responses (n=95)**

### **4.3.2 *Adverse Events***

There was one serious adverse event that resulted in the death of one participant, which was unrelated to the study. Six participants experienced adverse events that were related to the study medication; most commonly cited were vivid dreams and disturbed sleep from overnight patch-use (n=5), and soreness/heavy arm at the site of the patch (n=1). Twelve participants experienced adverse events that were unrelated to the study e.g. flu-like symptoms, bacterial infections.

## **4.4 Discussion**

It took seven months to gain the necessary NHS regulatory approvals to run the trial, in addition to five months to identify practices and train the study team. A response rate of 2.9% was achieved with an overall recruitment rate of 2.5%. In total, 137 participants were enrolled into the study, of which 119 were randomised. Delays with NHS regulatory approvals meant that there was insufficient time to recruit the desired 200 participants into the study. Moreover, the response rate was lower than the 5-10% originally forecast by recruiting through GP practices. While efforts were made to improve recruitment by increasing the number of sites, targeting a new population group and using new advertising methods, it was not possible to reach the target sample size within the available timescale.

Attrition rates were similar across groups, with most people dropping out early in the treatment programme because they had abandoned their quit attempt. Attendance rates were high, as were the number of retraining sessions adhered to, indicating that the

intervention was feasible to carry out within stop smoking clinics despite initial barriers to recruitment.

There is limited evidence on what recruitment strategies are effective for enrolling participants into smoking cessation programmes (Belisario et al., 2012) and into randomised controlled trials in general (Treweek et al., 2013). The former review found that tailored, proactive and more intensive methods of recruitment are more effective than less personal, reactive and less intensive strategies. For example, personal telephone calls are more effective than invitation letters (RR=40.73, 95% CI=2.53, 654.74) as are more phone call attempts (RR=1.87, 95% CI=1.61, 2.18). Similarly, Treweek et al. (2013) found that telephone reminders to non-responders were effective in increasing recruitment of participants into trials (OR=1.95, 95% CI=1.04, 3.66), in addition to ‘opt-out’ versus ‘opt-in’ procedures (RR=1.39, 95% CI=1.06, 1.84) in which participants are enrolled automatically unless they request otherwise. While these methods may improve recruitment rates, increasing the number of calls and reminders has clear cost implications and opt-out procedures are ethically controversial.

Although we did not achieve the desired number of participants, this study is larger than the other smoking attentional retraining studies (e.g. Attwood et al. (2008) n=55, Field et al. (2009b) n=72, McHugh et al. (2010) n=64].

Regarding the acceptability of the intervention, most participants reported that they would use AR procedures if it helped them stop smoking, although some commented that the length of the task was too long and boring. As found in the laboratory study in Chapter 2, it is difficult to ascertain what constitutes a tolerable length of training as this must be determined in part by its ability to produce a retraining effect. The Alcohol Attention-Control Training Program (AACTP) procedure developed by Fardardi and Cox (2009) that trained harmful and hazardous drinkers to attend away from alcohol-related stimuli had an interactive component to its program, in which participants were able to play an active role in the design by choosing which neutral soft drinks to be trained towards. Participants also received feedback on the number of correct responses and were encouraged to be quicker on subsequent trials. Both active participation and positive feedback may increase engagement in AR procedures and reduce the effects of boredom. Furthermore, many of the tasks used in smoking retraining studies rely on somewhat outdated visual graphics created over a decade ago; in light of technological advancements there is scope to upgrade the displays, which might enhance the visual appeal of such tasks.

The intervention was both feasible and acceptable to deliver within NHS stop smoking clinics. Initial delays in obtaining NHS regulatory approvals and the poor response rate to our recruitment methods meant that we were unable to recruit enough people in the time available. Attendance at clinic sessions was high and patients completed most training sessions. Overall, most participants were satisfied with the computer task, despite some experiencing boredom. If attentional retraining procedures are clinically effective in treating addictions, compliance with such tasks - that use a computer interface - may be

enhanced by incorporating active user-involvement or by improving visual features of the design.

# **CHAPTER 5: A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL OF ATTENTIONAL BIAS RETRAINING IN CIGARETTE SMOKERS ATTEMPTING SMOKING CESSATION (ARTS) – TRIAL FINDINGS**

## **5.1 Introduction**

The penultimate chapter of this thesis meets the second and third objective of the ARTS trial: to report on the efficacy of an AR intervention on attentional bias and smoking cessation outcomes; and to investigate the association between attentional bias, urges to smoke, withdrawal and relapse in smokers.

The following trial outcomes (as discussed in the protocol, section 3.3) were assessed and compared across each trial arm, using an intention-to-treat analysis:

- Post-training attentional bias on the visual probe task and pictorial Stroop task;
- The strength of weekly urge to smoke and withdrawal symptoms;
- Abstinence rates;
- Time to first lapse;
- Change in cue-induced craving;
- The strength of weekly urge to smoke and withdrawal symptoms at follow-ups;
- Post-training bias on the visual probe task and pictorial Stroop task at follow-ups
- Post-training attentional bias towards untrained novel stimuli;

Across all participants, the following observational outcomes were assessed:

- The association between baseline attentional bias and nicotine dependence
- The association between baseline attentional bias and urges to smoke
- The association between baseline attentional bias and withdrawal symptoms
- The association between attentional bias and smoking abstinence

Data for the six month follow-up outcome have been omitted as these were not available at the time of writing; therefore the results that follow include analyses up to the three month follow-up.

## **5.2 Statistical analyses**

### **5.2.1 Primary analyses**

Attentional bias scores on the visual probe task were calculated in the following way. An RT was produced for each correct response made on each trial where the probe replaced either the smoking-related picture or neutral picture. A median RT was calculated for all RTs produced for smoking-related pictures and all RTs produced for neutral pictures. A score for attentional bias was calculated by subtracting the overall median RT to smoking-related pictures from the median RT to neutral pictures, with positive scores indicating a bias towards smoking cues and negative scores indicating a bias towards neutral cues. Median RTs were used because distributions of mean RTs are often reported as skewed (MacLeod et al., 2002; Schoenmakers et al., 2010); therefore we did not need to set parameters for outlying RTs. Bias scores, as measured at four weeks post-quit, were used to examine retraining effects on attentional bias firstly by trial arm and secondly by



abstinence status using ANCOVA. An alpha level of 0.05 was employed. Bias scores were analysed as a complete case in the first instance and secondly, after imputation of missing RTs via regression of available data points. This was carried out by fitting a quadratic term of time and time<sup>2</sup> to each participants' observed RT scores, where the predicted value from the regression was used if there was a missing measurement. Values were only imputed if the missing RT was between time points with an observed value in order to avoid extrapolating beyond the observed data, i.e. imputation was not carried out if the baseline RT was missing or if the participant had no measurements after the four week visit or eight week follow-up. These analyses were performed using PASW Statistics 18 (SPSS, Inc., 2009, Chicago, IL, USA).

To investigate retraining effects on weekly urge to smoke, data were analysed using mixed effects regression models with an autoregressive variance-covariance structure, to allow for variations in craving between participants. This enabled all weekly time points to be included and modelled simultaneously. This modelling technique was used for MPSS scores; as mentioned in section 3.2.7.1, composite scores for urge to smoke (MPSS-C) and withdrawal symptoms (MPSS-M) were calculated. Regression coefficients, p-values and 95% confidence intervals (CI) were derived from the models. These analyses were undertaken using Stata 11.0 (StataCorp, 2009, College Station, TX: StataCorp LP).

Intention-to-treat analyses were performed to account for people who dropped out of treatment.

### 5.2.2 *Secondary analyses*

To examine the effects of AR on withdrawal symptoms, the same modelling technique as mentioned in section 5.2.1 for MPSS-C scores was used for MPSS-M scores.

To determine the proportion of people achieving abstinence by trial arm, risk ratios (RRs) were calculated with corresponding 95% CIs. Those reported as lost-to-follow up were counted as non-abstinent, as is standard in the reporting of smoking cessation trials (Hughes et al., 2004b; West et al., 2005).

Proportional hazards modelling was used to analyse the median time to lapse by trial arm; hazard ratios (HRs) are reported with corresponding 95% CIs. These analyses were performed using Stata 11.0 (StataCorp, 2009, College Station, TX: StataCorp LP).

#### 5.2.2.1 *Statistical modelling of MPSS-C and MPSS-M scores*

Two independent, fully specified, mixed-effects regression models of craving (MPSS-C) and withdrawal (MPSS-M) as outcome variables against the explanatory variables of time, group (attentional retraining/control) and abstinence status (non-abstainers/abstainers) were constructed. Time was kept as a continuous variable. In all models, the reference categories were the attentional retraining group and abstainers. Participant ID was treated as the random effects part of the models. Missing values for MPSS-C and MPSS-M scores were imputed as last observation carried forward, where

the last known value for a given item on the weekly questionnaire was used to fill in a subsequent missing data point (e.g. if a rating for craving had been completed at three weeks post-quit but not at four weeks, this last rating was “carried forward”).

For MPSS-C scores, post-quit raw urge scores were modelled without inclusion of baseline scores as suggested by West and Hajek (2004) because urges to smoke experienced during ad lib smoking are likely to be different to those experienced during abstinence. The time points for assessments therefore included quit day, one week post-quit, two weeks post-quit, three weeks post-quit and four weeks post-quit.

As quit-related withdrawal differs from the general anxiety often felt by some smokers prior to quit day, baseline scores for the MPSS-M were included as a covariate in the model for withdrawal symptoms, which also allowed for correction of variations in scores between subjects (Shiffman et al., 2004b). Baseline MPSS-M scores measured prior to quit day on two measurement occasions were totalled, averaged and then entered as a covariate into the model.

In order to examine the effects of AR on urge to smoke and withdrawal over time, it was necessary to include interaction terms involving time. The model was checked by comparing the plots of the observed and predicted means. If a large difference was found between the observed and predicted means, a time squared term and time cubed term was

added to see if the fit of the model was significantly improved. Quadratic models have been found to best fit models of craving and withdrawal (Piasecki et al., 2003).

The fully specified models of MPSS-C and MPSS-M scores included all main effects, lower order two-way interactions and a three-way interaction between time, group, and abstinence status. Stepwise regression was carried out using backward elimination to remove interactions that failed to reach the significance threshold ( $p < 0.05$ ). Additionally, model comparisons were performed using chi squared to assess goodness of fit and qualify the removal of any interactions. These steps were followed to produce the most parsimonious models of MPSS-C and MPSS-M scores to best explain the data.

The parsimonious models of the MPSS-C and MPSS-M were used to produce linear combinations of the coefficients in order to estimate the overall effect of AR on urge to smoke and withdrawal symptoms between groups and by abstinence status over time. As per protocol, the overall treatment effect is reported in abstainers initially and reported in non-abstainers separately.

To minimize over-fitting, the most parsimonious models were used in all exploratory analyses. At each step of modelling, diagnostic checks were carried out on the residuals of each model using scatter plots to check normality. Box and whisker plots were constructed to check the distribution of scores.

### 5.2.3 *Ancillary analyses*

We examined the effects of AR on attentional bias, MPSS-C scores and MPSS-M scores at eight weeks and three months post-quit to investigate longer-term retraining effects. The same modelling technique was used as in the analysis of the four week post-quit data, unless otherwise stated in the corresponding sections.

We adjusted the analyses of attentional bias scores, MPSS-C scores and MPSS-M scores for potential moderators of attentional bias, urge to smoke and withdrawal symptoms. Demographic and clinical characteristics were entered as covariates into linear regression models of attentional bias scores and into the most parsimonious model of urge to smoke and withdrawal to examine any interaction effects. These included age, gender and FTND across all analyses. Pre-quit urge to smoke was also examined in the model of attentional bias scores and pre-quit attentional bias in the models of MPSS-C and MPSS-M.

To examine retraining effects on cue-induced craving, VAS scores were analysed in a mixed-effects regression model; the same modelling technique that was used for MPSS-C and MPSS-M scores (section 5.2.2.1) was carried out again in this instance.

Visual analogue scale scores were calculated from measurements taken from a 0-100 mm scale before and after the cue exposure task, which was administered one week before quit day and again at four weeks, eight weeks and three months post-quit. The difference

between pre and post measurements was calculated and the change in cue-induced craving over time is reported.

Generalization of AR to other cognitive bias measures was assessed using RT scores from the pictorial Stroop task. Stroop bias scores were calculated by subtracting median RTs to probes that replaced neutral pictures from median RTs to probes that replaced smoking-related pictures. Slower RTs towards smoking-related pictures indicated a bias towards smoking cues. Again, parameters for outlying RTs did not need to be defined as median rather than mean RTs were used. Bias scores, as measured at four weeks post-quit, were used to examine retraining effects on Stroop bias firstly by trial arm and secondly by abstinence status using ANCOVA.

Similarly, we assessed whether AR could generalize to untrained novel stimuli that only appeared in the assessment versions of the visual probe task and not during training sessions. Attentional bias scores for the trained and untrained stimuli were therefore analysed separately using ANCOVAs.

Finally, we compared the number of participants who correctly identified their group allocation by trial arm, based on whether participants thought that they were allocated to the training group/allocated to no training group/unsure of group allocation.

#### **5.2.4 *Observational data analyses***

To facilitate our understanding of attentional bias, we further examined whether attentional bias was associated with measures of nicotine dependence, including FTND and smoking rate (cigarettes per day), using linear regression. Similarly, we investigated associations between attentional bias and our clinical outcomes of interest; mixed-effects linear regression models were constructed to examine urge to smoke and withdrawal symptoms as outcome variables prior to and post quitting, with period of quit attempt treated as a categorical variable (pre-quit/post-quit). Logistic regression was used to examine the predictive validity of attentional bias measures on four weeks abstinence. Odds ratios (OR) and 95% confidence intervals (CI) are reported in these cases. In all analyses outlined in this section, we tested associations using both cognitive task measures (visual probe task and pictorial Stroop task) to examine the predictive utility of each measure.

### **5.3 Results**

#### **5.3.1 *Baseline characteristics***

Of the 196 participants who were initially screened, 119 were randomly allocated to either AR or control. One randomised participant died during the trial; data were subsequently excluded for this participant as recommended in intention-to-treat analyses for outcomes in cessation trials (West et al., 2005). Demographic and clinical characteristics are therefore reported for n=118 participants.

The sample was predominantly female, white British and middle-aged (Table 14). Approximately half were in employment. Less than half had a higher level professional qualification. Participants were moderately dependent and smoked approximately 20 cigarettes a day (Table 15). As expected from a RCT design, there were no group differences in baseline characteristics.



**Table 14. Demographic characteristics of participants**

	All (n=118)	Attentional retraining (n=60)	Control (n=58)
Age in years mean (SD)	44.8 (12.7)	46.5 (12.7)	43.0 (12.7)
Gender ratio (M:F)	49:69	26:34	23:35
Ethnicity n (%)			
White-British	92 (78.0)	46 (76.7)	46 (79.3)
White-Irish	3 (2.5)	3 (5.0)	-
White-other	1 (0.8)	1 (1.7)	-
White & Black Caribbean	7 (5.9)	4 (6.7)	3 (5.2)
White & Black African	-	-	-
White & Asian	1 (0.8)	-	1 (1.7)
Mixed-other	4 (3.4)	1 (1.7)	3 (5.2)
Indian	1 (0.8)	-	1 (1.7)
Pakistani	1 (0.8)	1 (1.7)	-
Bangladeshi	-	-	-
Asian other	1 (0.8)	1	-
Caribbean	4 (3.4)	1 (1.7)	3 (5.2)
African	-	-	-
Black-other	2 (1.7)	2 (3.3)	-
Chinese	1 (0.8)	-	1 (1.7)
Any other ethnic group	-	-	-
Employment n (%)			
Employed	61 (51.7)	27 (45.0)	34 (58.6)
Unemployed	17 (14.4)	9 (15.0)	8 (13.8)
Looking after home or family	11 (9.3)	4 (6.7)	7 (12.1)
Student	3 (2.5)	1 (1.7)	2 (3.4)
Retired	14 (11.9)	10 (16.7)	4 (6.9)
Long-term sick or disabled	9 (7.6)	6 (10.0)	3 (5.2)
Other	3 (2.5)	3 (5.0)	-
Highest Education n (%)			
No formal qualifications	32 (27.1)	12 (20.0)	20 (34.5)
Other qualifications below 'A' level/vocational level 3	36 (30.5)	19 (31.7)	17 (29.3)
'A' levels/vocational Level 3 a above	23 (19.5)	14 (23.3)	9 (15.5)
Degree, or equivalent/above	21 (17.8)	11 (18.3)	10 (17.2)
Other Qualifications	6 (5.1)	4 (6.7)	2 (3.4)

**Table 15. Clinical characteristics of participants**

	All (n=118)	Attentional retraining (n=60)	Control (n=58)
	M (SD)	M (SD)	M (SD)
Cigarettes smoked per day	20.83 (9.24)	21.80 (9.88)	19.83 (8.49)
Age started smoking (years)	16.49 (4.35)	16.62 (4.03)	16.35 (4.69)
FTND*	5.52 (2.26)	5.33 (2.44)	5.72 (2.06)
MPSS-C at baseline	10.67 (2.29)	10.73 (2.10)	10.62 (2.49)
MPSS-M at baseline	20.10 (8.62)	21.53 (8.60)	18.64 (8.45)
VAS craving at baseline	40.40 (28.65)	37.33 (28.88)	43.70 (28.30)

\*Fagerstrom Test for Nicotine Dependence, scored from 0-10.

### 5.3.2 Data reduction

Of the 118 participants, 98% contributed to visual probe task data at the baseline assessment; 73% at four weeks; 75% at eight weeks and 69% at three months. Data from 2, 6, 0 and 3 participants were lost due to computer/experimenter error at baseline, four weeks, eight weeks and three months respectively. The remaining participants who did not contribute to follow-up data dropped out of treatment (see section 4.2.4, Participant flow, Figure 17).

A total of 118 (100%) participants completed pictorial Stroop assessments at baseline; 75% at four weeks; 72% at eight weeks and 69% at three months. Due to computer/experimenter error, data were lost from 0 participants at baseline, 4 at four weeks, 3 at eight weeks and 3 at three months. Trials with errors were also removed from pictorial Stroop task data; the error rate was 2.1% at baseline, 2.3% at 4 weeks, 2.3% at eight weeks and 2.2% at three months.

Imputation was carried out in cases where data were either lost due to experimenter/computer error or absent due to missed clinic visits between follow-up assessments. Visual probe task data were imputed in 9 cases at four weeks, 7 cases at eight weeks and 13 cases at three months. For Stroop task data, 8 cases were imputed at four weeks, 10 cases at eight weeks and 13 cases at three months. These analyses are reported separately in section 5.3.5.1 and 5.3.14.3.

### **5.3.3 *Attentional bias at baseline***

Participants across both groups did respond faster in the predicted direction towards smoking-related pictures than neutral pictures at baseline (mean difference=3.21).

However, a one-sample t-test against zero indicated that this difference was not significant ( $t[115]=1.16$ ,  $p=0.25$ ).

### **5.3.4 *Effects of attentional retraining on attentional bias***

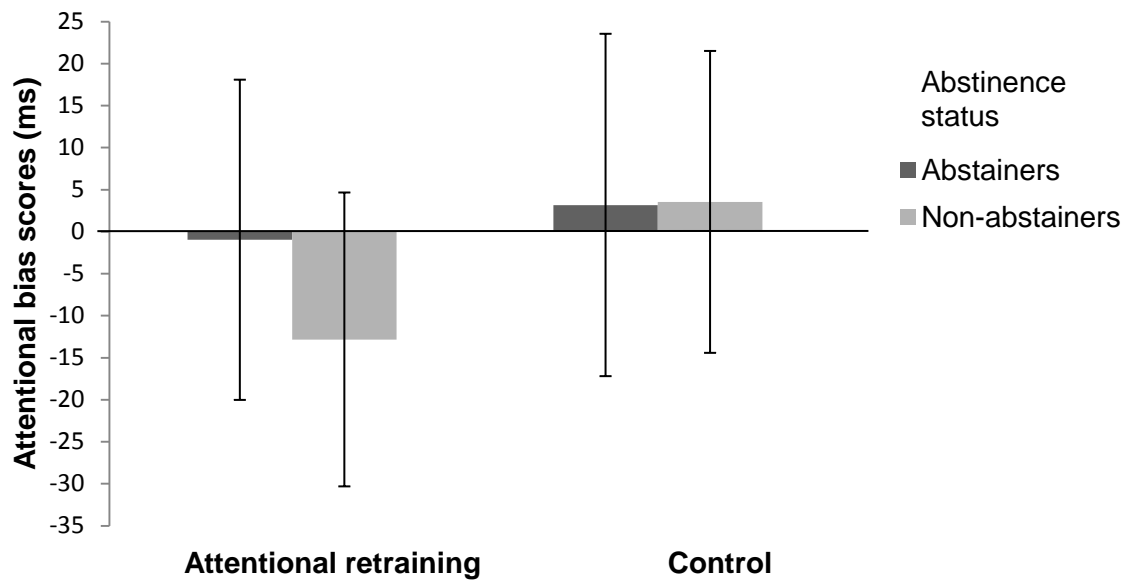
Mean attentional bias RT scores by trial arm are shown in Table 16. To examine whether there were any group differences in attentional bias scores at 4 weeks post-quit, a one-way between groups ANCOVA was performed while adjusting for pre-training attentional bias scores. No significant differences were found between groups in post-training attentional bias scores ( $F[2,81]=2.66$ ,  $p=0.12$ ). Similarly, when a 2 x 2 between-groups ANCOVA was performed with abstinence status included, there were no significant main effects or interactions ( $F_s < 3.08$ ,  $p_s > 0.1$ ).

**Table 16. Pre-training and post-training attentional bias scores at 4 weeks, 8 weeks and 3 months by trial arm**

	Attentional retraining (n= 58)	Control (n=58)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	684.36 (153.52)	684.71 (130.59)	-0.34	-0.01	0.99	(-52.77, 52.08)
RT for neutral stimuli	685.33 (158.84)	690.16 (133.81)	-4.84	-0.18	0.86	(-58.86, 49.19)
Attentional bias	0.97 (24.28)	5.46 (34.49)	-4.49	-0.81	0.42	(-15.46, 6.48)
Post-training +4 week						
RT for smoking stimuli	688.54 (134.43)	655.01 (136.50)	33.53	1.15	0.26	(-24.68, 91.74)
RT for neutral stimuli	683.02 (125.99)	658.26 (141.04)	24.75	0.86	0.39	(-32.50, 82.02)
Attentional bias	-5.52 (28.05)	3.25 (21.04)	-8.77	-1.62	0.11	(-19.54, 1.99)
Post-training +8 week						
RT for smoking stimuli	672.13 (129.73)	657.15 (117.12)	14.98	0.57	0.57	(-37.47, 67.44)
RT for neutral stimuli	672.87 (125.15)	651.78 (116.82)	21.09	0.82	0.42	(-30.28, 72.45)
Attentional bias	0.73 (24.96)	-5.37 (24.42)	6.11	1.16	0.25	(-4.37, 16.58)
Post-training 3 months						
RT for smoking stimuli	683.57 (155.95)	666.68 (135.54)	16.90	0.52	0.60	(-47.45, 81.25)
RT for neutral stimuli	683.00 (156.53)	668.80 (135.26)	14.20	0.44	0.66	(-50.23, 78.63)
Attentional bias	-0.57 (29.93)	2.13 (22.91)	-2.70	-0.46	0.65	(-14.45, 9.06)

*RT - reaction time (milliseconds)*

While no statistical significance was found, an analysis within abstainers and non-abstainers across groups was also performed. Closer inspection of the point estimates for only abstainers indicated that attentional bias scores were lower in the AR group than the control group post-training ( $\beta=-4.15$ ,  $p=0.56$ , 95% CI=-18.29, 10.00). Similarly in non-abstainers, bias scores were 16.37 points less in the AR group compared to the control group ( $p=0.07$ , 95% CI=-34.23, 1.50; see Figure 19).



**Figure 19. Attentional bias scores (ms) with 95% CI by abstinence status in the attentional retraining group (n=58) and control group (n=58)**

#### 5.3.4.1 Effects of attentional retraining on attentional bias – imputed dataset

Using imputed scores for missing RT data, group differences in attentional bias scores at four weeks post-quit were assessed again in a one-way between groups ANCOVA adjusted for pre-training attentional bias scores. As found previously, no significant differences were found between groups in post-training attentional bias scores ( $F[2,92]=2.01$ ,  $p=0.16$ ). Similarly, in a 2 x 2 between-groups ANCOVA with abstinence status included, no significant main effects or interactions were found ( $F_s < 2.23$ ,  $p_s > 0.14$ ).

#### *5.3.4.2 Effects of attentional retraining on attentional bias at 8 weeks and 3 months post-quit*

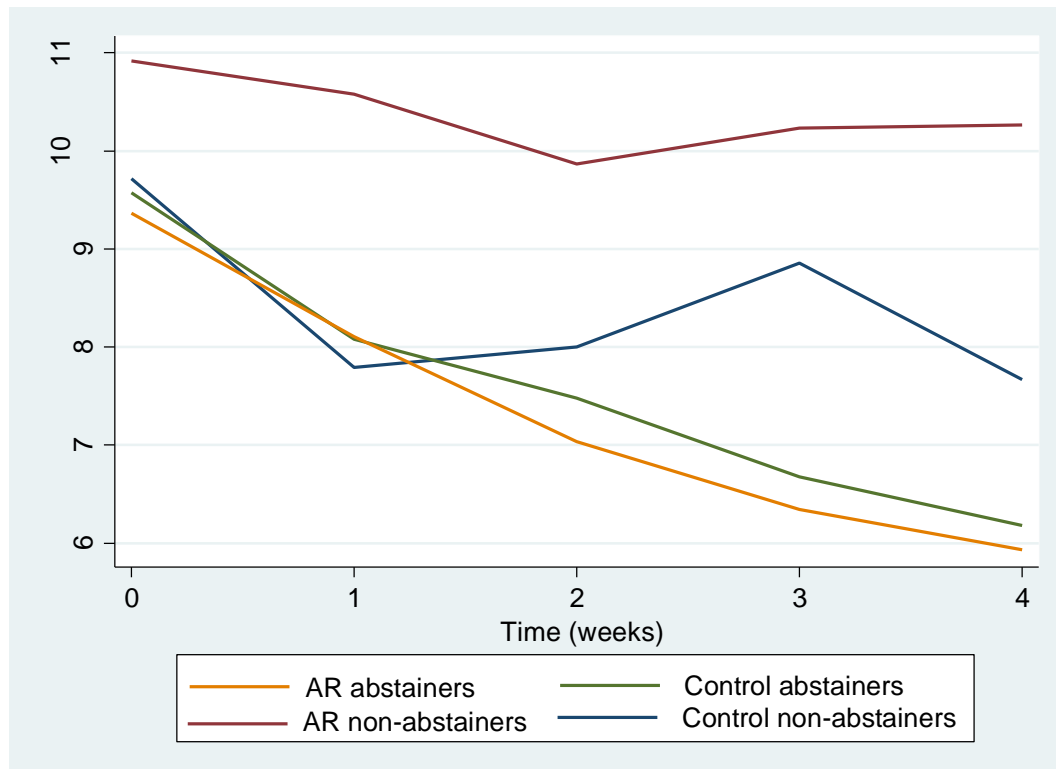
The t-test results for the 8-week and 3-month post-training attentional bias scores in Table 16 revealed no significant differences in bias scores by trial arm at either follow-up; as non-significant effects were seen at four weeks post-quit in the ANCOVAs performed in section 5.3.4, it was unlikely that any effects would be observed at later time points.

Therefore further analyses of these data have been omitted here, and in the analyses of 8-week and 3-month pictorial Stroop bias scores in section 5.3.13.

### ***5.3.5 Effects of attentional retraining on craving***

#### *5.3.5.1 MPSS-C at 4 weeks post-quit*

Mean scores for the MPSS-C by trial arm and abstinence status over time are illustrated in Figure 20. In abstainers across both groups, there was a general decrease in craving over time. In non-abstainers, scores were higher than in abstainers and were relatively stable over time.



**Figure 20. Mean MPSS-C scores by trial arm and abstinence status from quit day to 4 weeks (n=118)**

The means and standard deviations of the basic model of MPSS-C scores - according to a linear function of time by trial arm - indicated that there was a difference between the observed and predicted means, which warranted the inclusion of a time squared term and time cubed term (Appendix 26). Visual inspection of the plots revealed that the predicted scores fitted better to the observed data with the addition of time squared (Appendix 27a) but not time cubed (Appendix 27b); as the difference between the coefficients and shape of the curves was minimal, time cubed was discarded from all subsequent models to avoid the risk of overfitting.

The most parsimonious mixed-effects model of MPSS-C scores was reached through elimination of non-significant three-way and two-way interactions between trial arm, abstinence status and time; a three-way interaction of trial arm, abstinence status and time squared; and a two-way interaction of trial arm by time squared (Table 17). Chi-squared tests indicated that there was no significant difference in the log likelihood values between the fully specified model and parsimonious model (Table 18).

Figure 21 illustrates a U-shaped pattern for the fixed-effects portion of predicted MPSS-C scores over time. Linear combinations of the coefficients indicated a 0.19 point reduction in craving among only abstainers in the AR group compared to the control group, although this difference was small and not statistically significant ( $p=0.74$ , 95% CI=-1.30, 0.93).

In a sub-group analysis of only non-abstainers, craving was significantly higher in the AR group compared to the control group ( $\beta=1.91$ ,  $p=0.003$ , 95% CI=0.67, 3.16).



**Table 17. Mixed-effects models of MPSS-C scores over time by trial arm and abstinence status**

Variable	Model 1		Model 2		Model 3		Model 4	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects								
Time	-1.86	0.08	-1.47	0.003	-1.36	0.005	-1.30	0.006
Time <sup>2</sup>	0.17	0.19	0.12	0.03	0.12	0.03	0.12	0.03
Treatment arm <sub>1</sub>	-1.69	0.53	0.74	0.52	1.52	0.09	1.10	0.003
Abstinence status <sub>2</sub>	-0.27	0.91	0.43	0.70	1.13	0.20	1.13	0.20
Intercept	12.76		12.09		11.68		11.47	
Interactions								
Treatment arm x Abstinence status	2.48	0.48	-0.77	0.61	-2.12	0.01	-2.10	0.01
Time x Abstinence status	0.09	0.94	-0.32	0.17	-0.50	0.002	-0.50	0.002
Time x Treatment arm	1.78	0.23	0.31	0.22	0.11	0.51		
Time x Treatment arm x Abstinence status	-2.30	0.22	-0.35	0.29				
Time <sup>2</sup> x Abstinence status	-0.05	0.76						
Time <sup>2</sup> x Treatment arm	-0.18	0.31						
Time <sup>2</sup> x Treatment arm x Abstinence status	0.25	0.30						
Random effects								
Participant ID, intercept (SD)	1.66		1.65		1.64		1.64	
-2*log likelihood	-1054.20		-1054.98		-1055.55		-1055.76	

*Model 1: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status*

*Model 2: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status*

*Model 3: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm*

*Model 4: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status*

*<sub>1</sub> Reference category is attentional retraining group, <sub>2</sub>Reference category is abstainers*

**Table 18. Difference in fit between models of MPSS-C scores over time**

	LL <sub>1</sub>	LL <sub>2</sub>	Chi squared	df	p
Model 1 to 2	-1054.20	-1054.98	0.78	3	0.85
Model 1 to 3	-1054.20	-1055.55	1.35	4	0.85
Model 1 to 4	-1054.20	-1055.76	1.56	5	0.91

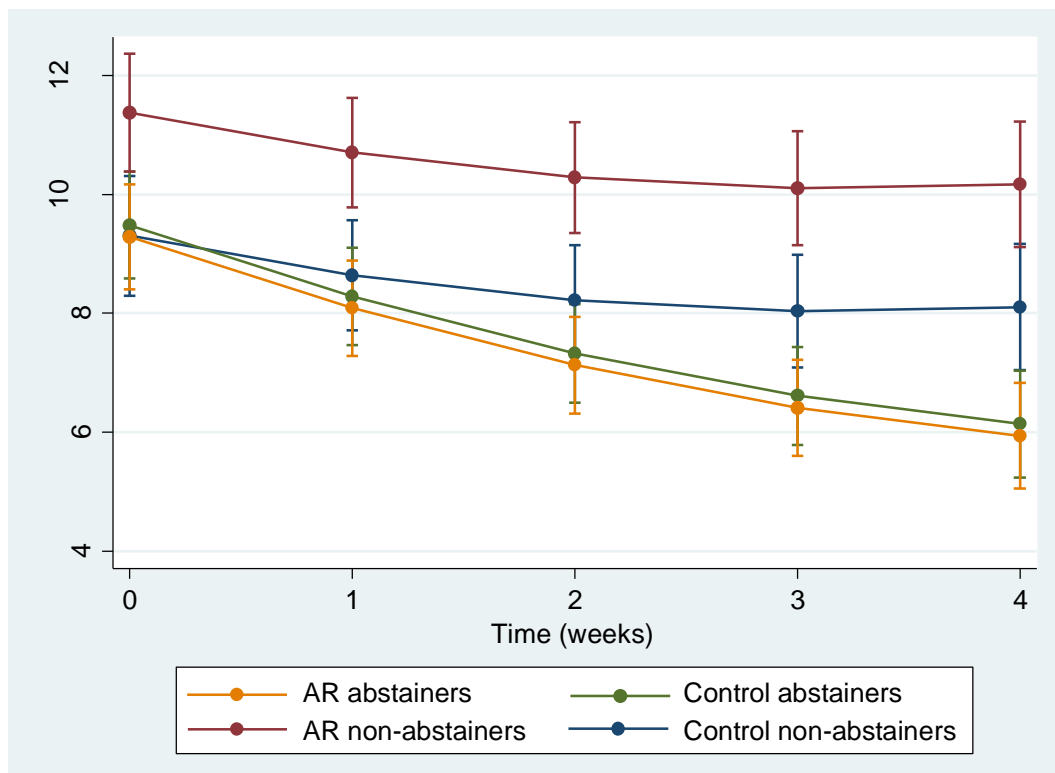
*Model 1: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status*

*Model 2: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status*

*Model 3: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm*

*Model 4: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status*

LL<sub>1</sub> - loglikelihood of hierarchically superior model; LL<sub>2</sub> - loglikelihood of comparison model

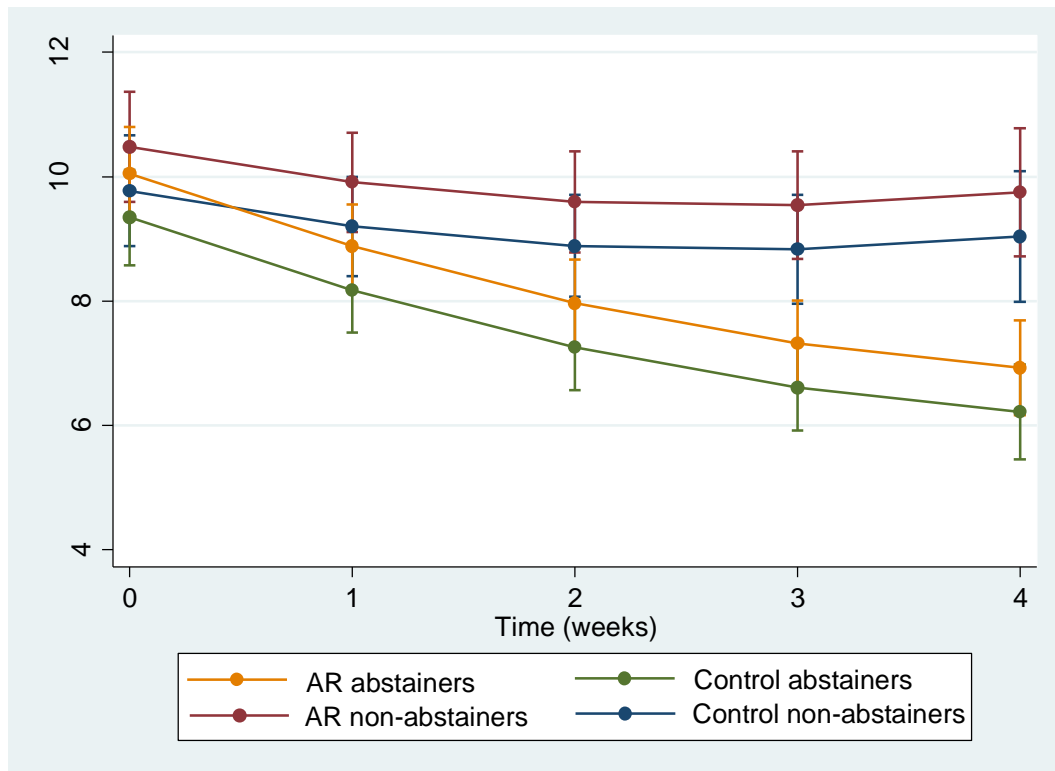
**Figure 21. Predicted MPSS-C scores (95% CI) by trial arm and abstinence status from quit day to 4 weeks (n=118)**

#### *5.3.5.1.1 Re-modelling of MPSS-C*

The urge to smoke profiles depicted in Figure 21 assume that there was no change in the abstinence status of participants during the 4-week period from quit day, as only the four week post-quit outcome for abstinence was used in the model. We re-analysed this data to take into account that a) the abstinence status of participants was likely to change during the course of their quit attempts and b) non-abstainers experienced higher levels of craving because they were still attempting to quit. Weekly abstinence (on quit day, one week post-quit, two weeks post-quit, three weeks post-quit and four weeks post-quit) was calculated from CO readings; a participant was deemed abstinent if their CO reading was recorded as <10 at each clinic visit.

A mixed-effects model of MPSS-C scores with three-way and two-way interactions involving trial arm, weekly abstinence status, time and time squared was constructed; only a two-way interaction between time and abstinence status remained in the model following backward elimination of all non-significant interactions (Appendix 28).

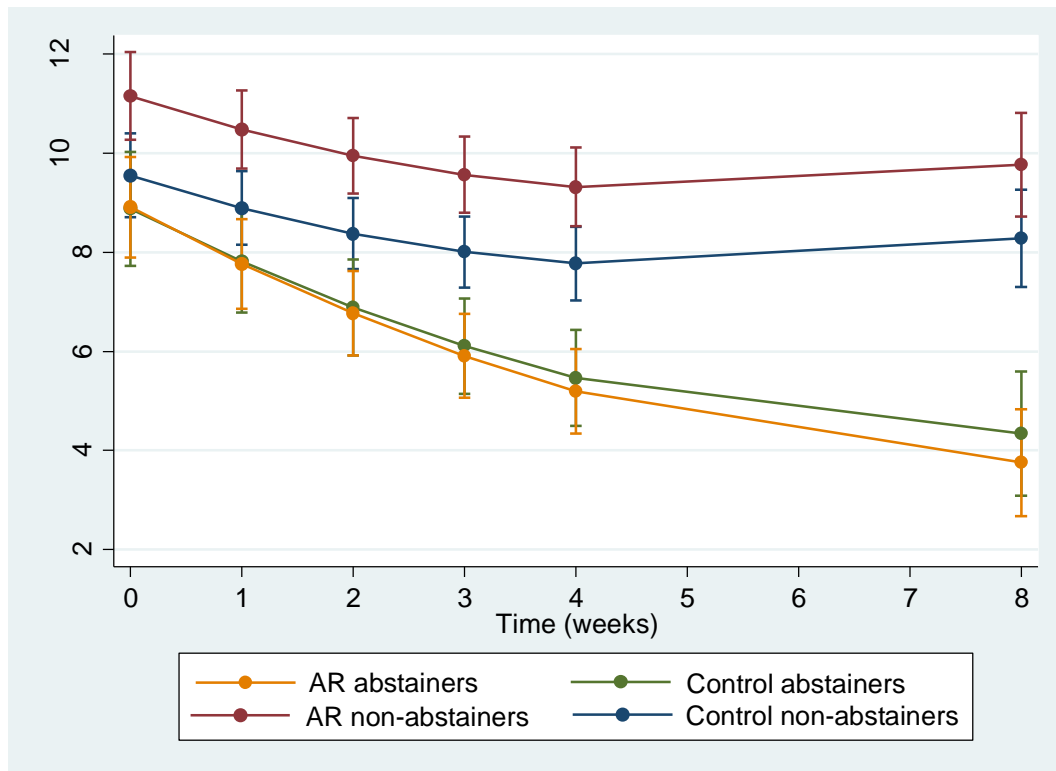
It is important to note that unlike the analysis of MPSS-C scores reported in section 5.3.5.1, different individuals were involved in this model at each time point because abstinence status was allowed to vary over time; however Figure 22 demonstrates that urge to smoke remained higher in those who were non-abstinent at each time point after quit day than in those who were abstinent.



**Figure 22. Predicted MPSS-C scores (95% CI) by trial arm and weekly abstinence status from quit day to 4 weeks (n=118)**

#### 5.3.5.2 MPSS-C at 8 weeks post-quit

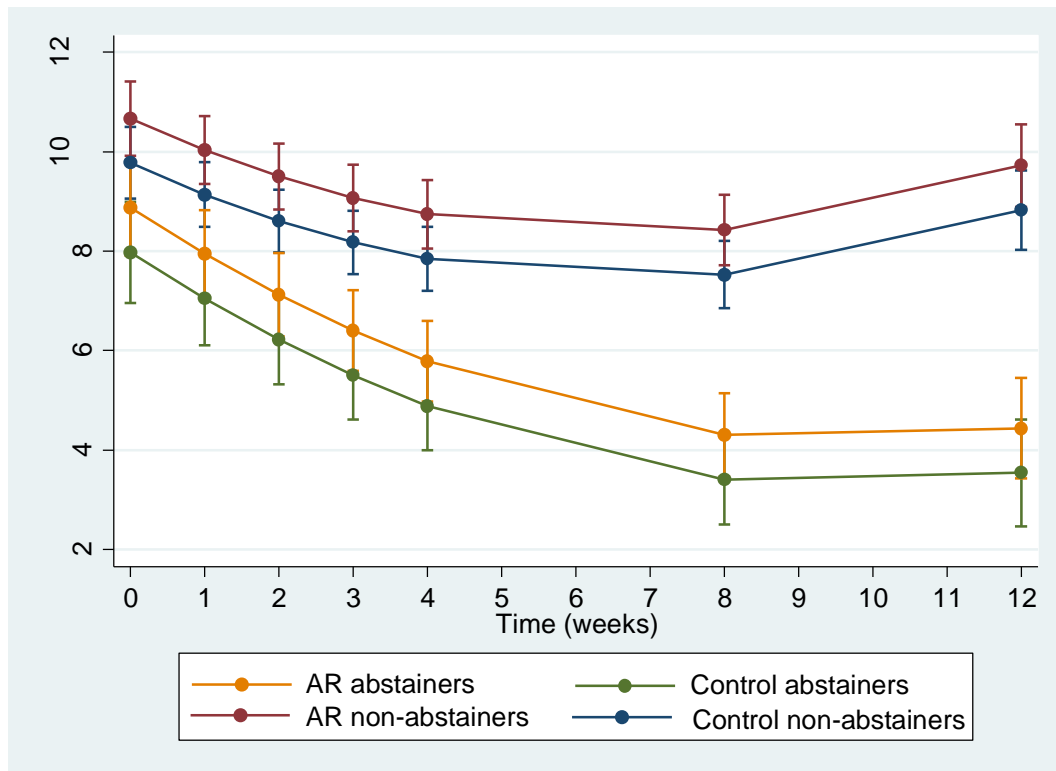
A mixed-effects model of MPSS-C scores at eight weeks post-quit indicated that across abstainers only, a 0.24 point non-significant reduction in craving was found in the AR group compared to the control group ( $p=0.70$ , 95% CI=-1.46, 0.99; Figure 23).



**Figure 23. Predicted MPSS-C scores (95% CI) by trial arm and weekly abstinence status from quit day to 8 weeks (n=118)**

#### 5.3.5.3 MPSS-C at 3 months post-quit

Unlike the parsimonious models to predict MPSS-C scores at four weeks and eight weeks post-quit, the model to predict MPSS-C scores at three months post-quit only contained a significant two-way interaction between time and abstinence status. Linear combinations of the coefficients indicated a significant 0.90 point increase in craving in the AR group compared to the control group ( $p=0.02$ , 95% CI=0.12, 1.68; Figure 24).

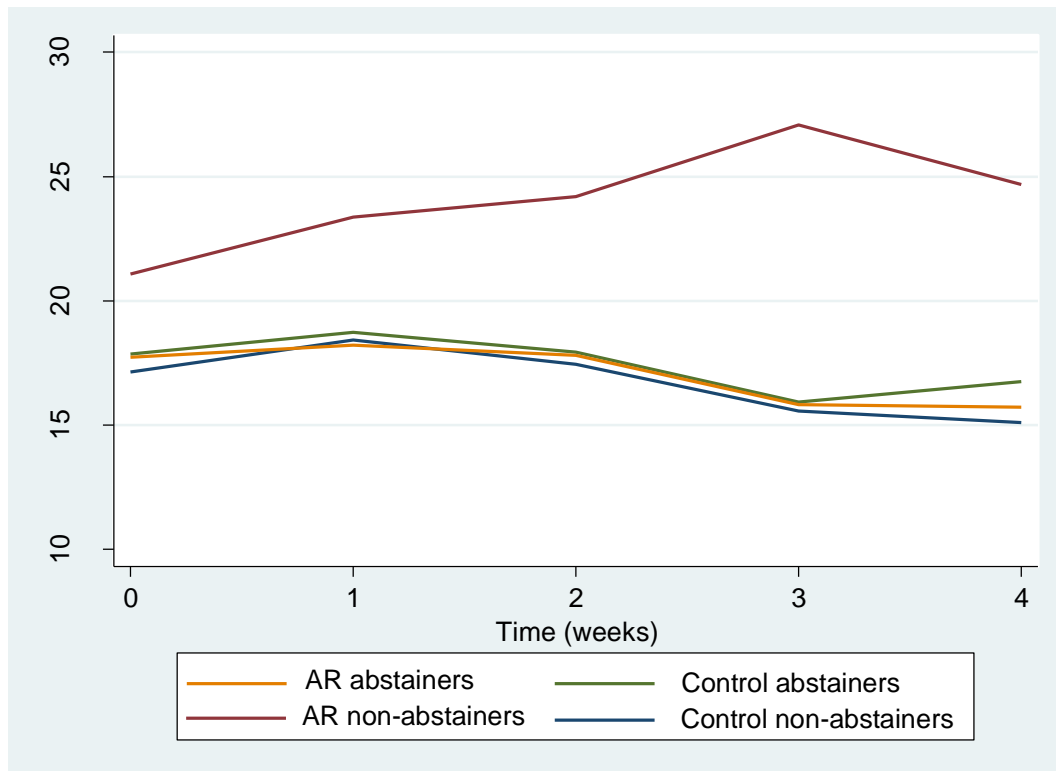


**Figure 24. Predicted MPSS-C scores (95% CI) by trial arm and weekly abstinence status from quit day to 3 months (n=118)**

### 5.3.6 Effects of attentional retraining on withdrawal symptoms

#### 5.3.6.1 MPSS-M at 4 weeks post-quit

The trajectory for withdrawal symptoms followed an inverted U-shaped pattern in both trial arms and among abstainers and non-abstainers. Withdrawal was generally higher in the AR group than the control group and in non-abstainers compared to abstainers. In abstainers, withdrawal scores declined steadily over time in contrast to an increase found in non-abstainers. Mean MPSS-M scores by trial arm and abstinence status are illustrated in Figure 25.

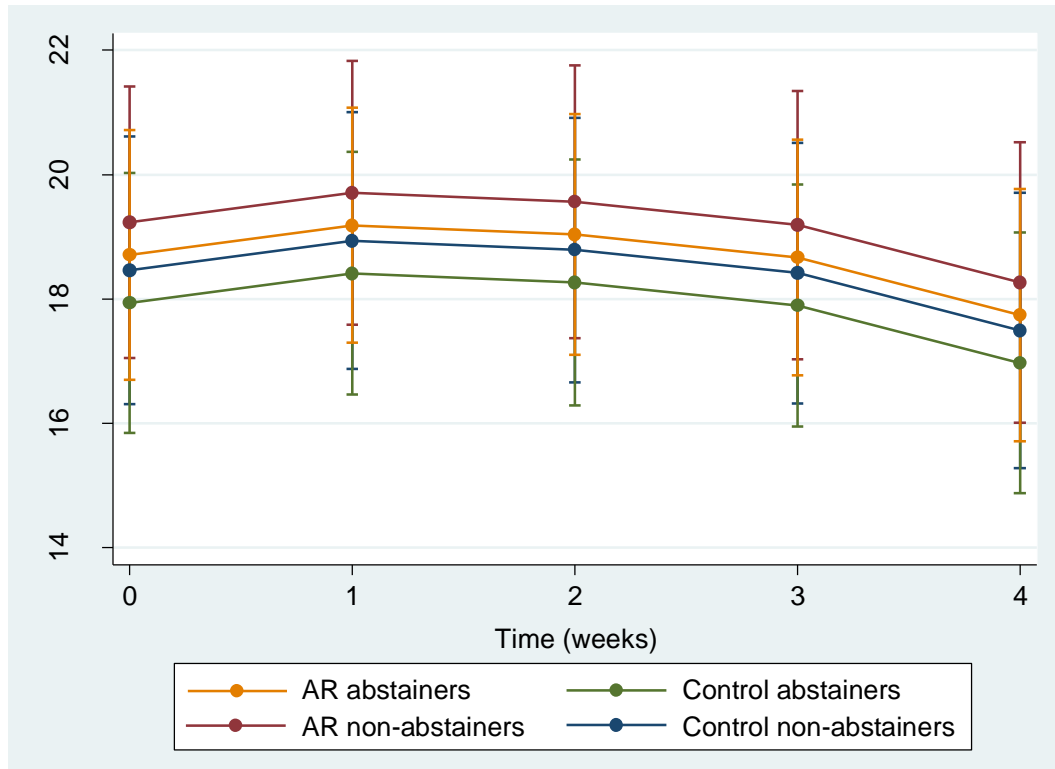


**Figure 25. Mean MPSS-M scores by trial arm and abstinence status from quit day to 4 weeks (n=118)**

As found in the mixed-effects model of MPSS-C scores, the predicted scores for the MPSS-M (Appendix 29) fitted better to the observed scores when time squared was included in the model (Appendix 30a) but not time cubed (Appendix 30b).

After adjusting for pre-quit MPSS-M scores, the fully specified model of MPSS-M scores revealed no significant three-way interactions or two-way interactions between trial arm, time or abstinence status (Table 19). Backward elimination of all interactions did not significantly reduce the log-likelihood of the model (Table 20). The most parsimonious model contained only a significant main effect of time squared, suggesting no difference in trend across trial arm or abstainers versus non-abstainers (Figure 26). The overall

treatment effect was a non-significant increase in withdrawal in the AR group compared to the control group ( $\beta=0.77$ ,  $p=0.50$ , 95% CI=-1.45, 2.98).



**Figure 26. Predicted MPSS-M scores (95% CI) by trial arm and abstinence status from quit day to 4 weeks (n=118)**



**Table 19. Mixed-effects models of MPSS-M scores over time by treatment arm and abstinence status**

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Variable	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects												
Baseline MPSS-M score	0.58	0.00	0.58	0.00	0.58	0.00	0.58	0.00	0.60	0.00	0.60	0.00
Time	3.95	0.13	1.85	0.13	2.26	0.06	2.45	0.04	2.43	0.04	2.07	0.08
Time <sup>2</sup>	-0.55	0.09	-0.29	0.05	-0.29	0.05	-0.29	0.05	-0.28	0.05	-0.29	0.05
Treatment arm <sub>1</sub>	-2.58	0.70	-1.83	0.52	1.10	0.62	2.43	0.16	0.78	0.49	0.77	0.50
Abstinence status <sub>2</sub>	6.69	0.28	0.65	0.81	3.26	0.14	3.26	0.14	1.86	0.33	-0.57	0.63
Intercept	0.40		3.97		2.39		1.67		2.11		3.47	
Interactions												
Time x Abstinence status	-3.51	0.30	0.04	0.94	-0.63	0.10	-0.64	0.10	-0.64	0.10		
Treatment arm x Abstinence status	3.07	0.72	2.04	0.59	-2.98	0.19	-2.91	0.21				
Time x Treatment arm	1.62	0.66	1.13	0.06	0.36	0.35						
Time x Treatment arm x Abstinence status	-1.97	0.68	-1.31	0.09								
Time <sup>2</sup> x Abstinence status	0.45	0.28										
Time <sup>2</sup> x Treatment arm	-0.06	0.89										
Time <sup>2</sup> x Treatment arm x Abstinence status	0.08	0.89										
Random effects												
Participant ID, intercept (SD)	4.77		4.76		4.77		4.79		4.85		4.77	
-2*log likelihood	-1484.51		-1485.91		-1487.34		-1487.77		-1488.57		-1489.88	

Model 1: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status

Model 2: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status

Model 3: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm

Model 4: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status

Model 5: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms time x abstinence status

Model 6: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status; <sub>1</sub> Reference category is attentional retraining group, <sub>2</sub> Reference category is abstainers

**Table 20. Difference in fit between models of MPSS-M scores over time**

	LL <sub>1</sub>	LL <sub>2</sub>	Chi squared	df	p
Model 1 to 2	-1484.51	-1485.91	1.40	3	0.71
Model 1 to 3	-1484.51	-1487.34	2.83	4	0.59
Model 1 to 4	-1484.51	-1487.77	3.26	5	0.66
Model 1 to 5	-1484.51	-1488.57	4.06	6	0.67
Model 1 to 6	-1484.51	-1489.88	5.37	7	0.61

*Model 1: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status*

*Model 2: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status*

*Model 3: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm*

*Model 4: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status*

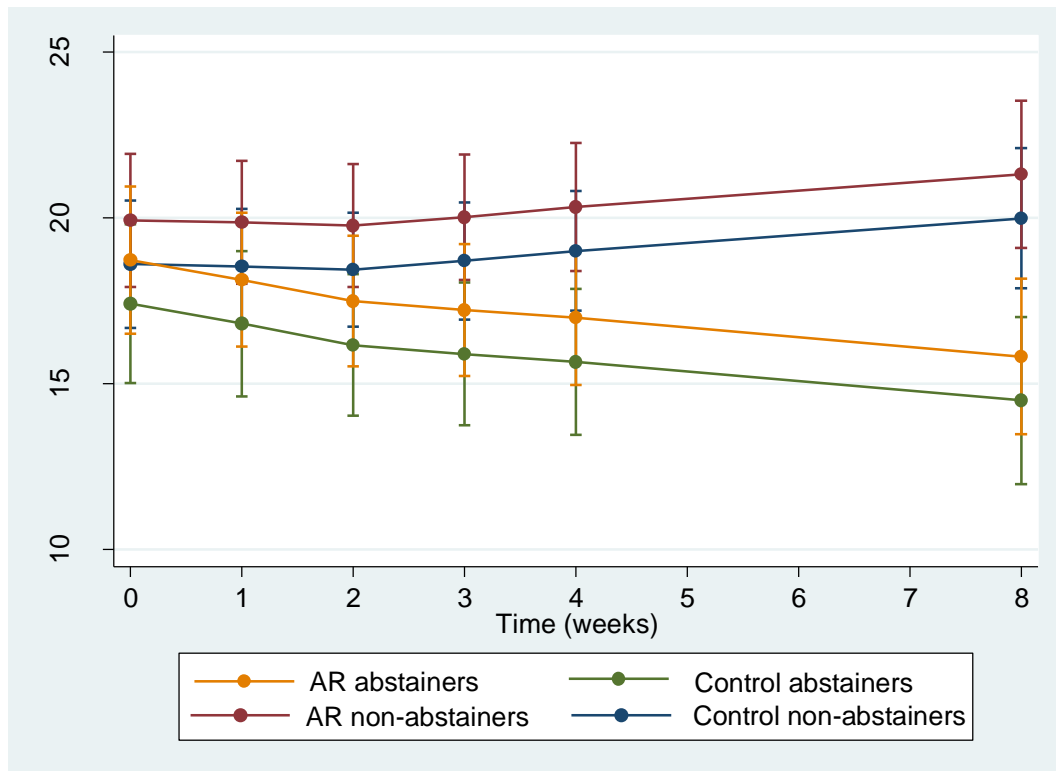
*Model 5: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms time x abstinence status*

*Model 6: Withdrawal scores by time, time<sup>2</sup>, treatment arm, abstinence status*

*LL<sub>1</sub> - loglikelihood of hierarchically superior model; LL<sub>2</sub> - loglikelihood of comparison model*

### 5.3.6.2 MPSS-M at 8 weeks post-quit

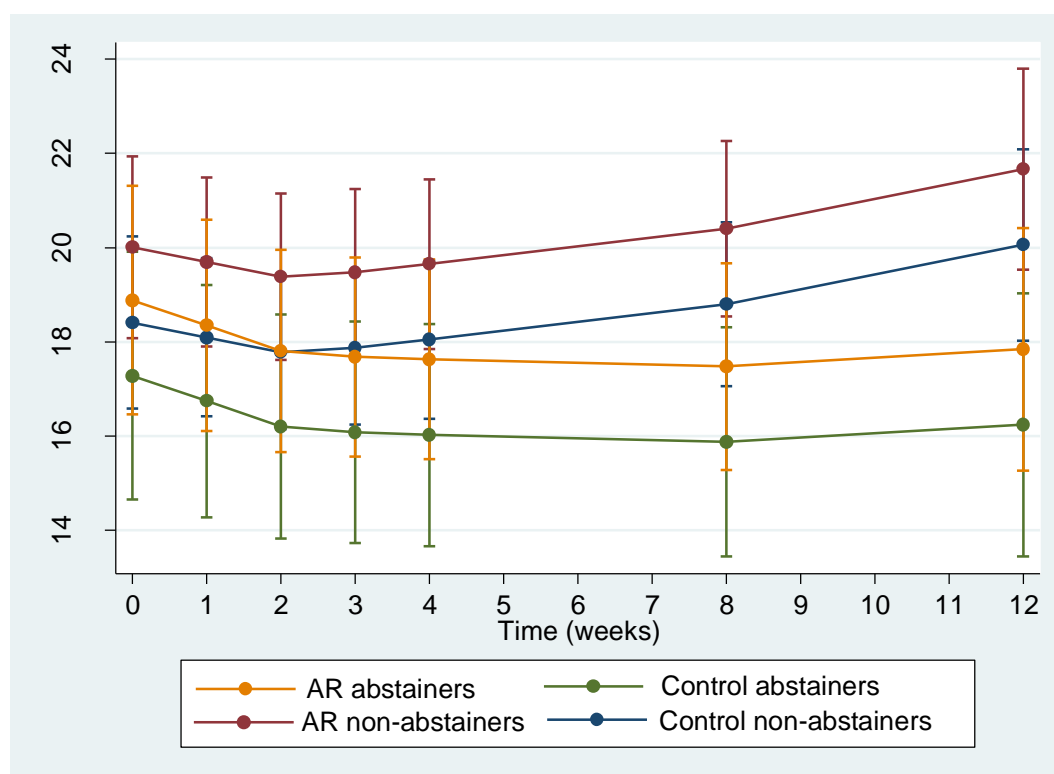
Only a significant two-way interaction between time and abstinence status remained in the most parsimonious mixed-effects model of MPSS-M scores at eight weeks post-quit; the overall treatment effect was a non-significant increase in MPSS-M score of 1.32 points in the AR group compared to the control group (p=0.22, 95% CI=-0.80, 3.45; Figure 27).



**Figure 27. Predicted MPSS-M scores (95% CI) by trial arm and abstinence status from quit day to 8 weeks (n=118)**

#### 5.3.6.3 MPSS-M at 3 months post-quit

Similar to the model of MPSS-M at four weeks post-quit, the model of MPSS-M at three months post-quit contained no significant three-way or two-way interactions between trial arm, abstinence status or time. As illustrated in Figure 28, the overall treatment effect was a non-significant increase of 1.59 points in the AR group compared to the control group ( $p=0.14$ , 95% CI=-0.50, 3.69).



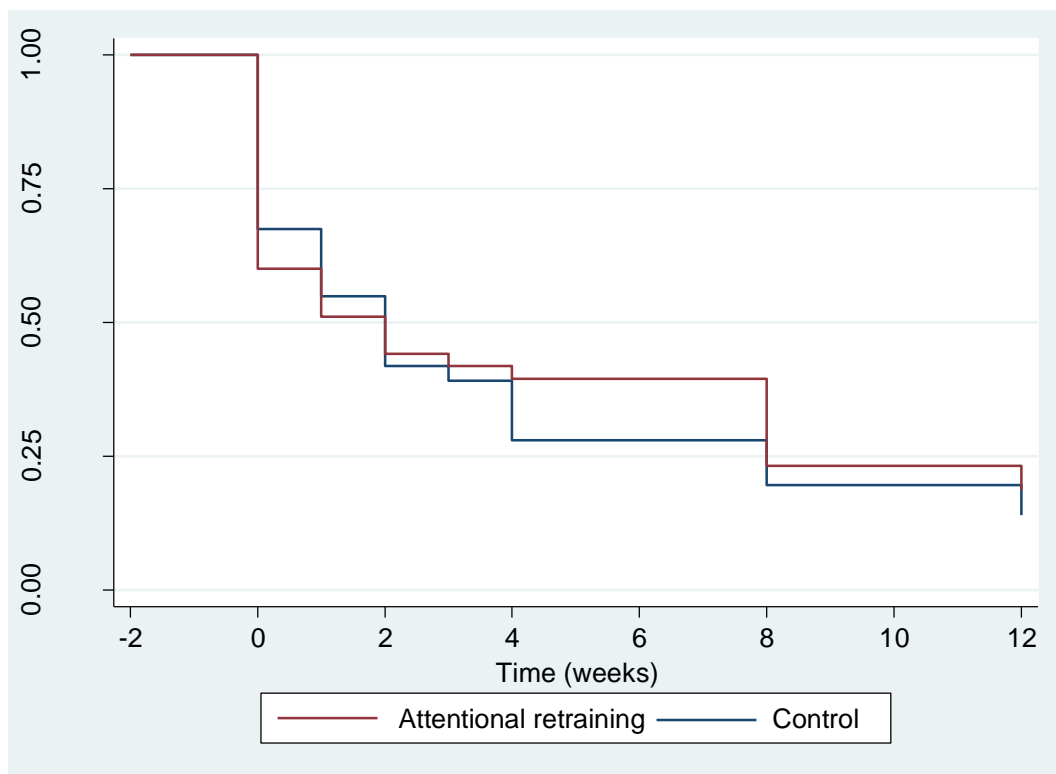
**Figure 28. Predicted MPSS-M scores (95% CI) by trial arm and abstinence status from quit day to 3 months (n=118)**

### 5.3.7 Effects of attentional retraining on abstinence

There was no significant difference between groups in the proportion of smokers achieving prolonged abstinence at four weeks post-quit; 30/60 achieved abstinence in the AR group and 29/58 in the control group (RR=1.00, 95% CI=0.70, 1.43). Quit rates were higher in the AR group compared to the control group at eight weeks, with 23/60 achieving abstinence in the AR group compared to 18/58 in the control group (RR=1.24, 95% CI=0.75, 2.04). At three months post-quit, 19/60 achieved abstinence in the AR group compared to 13/58 in the control group (RR=1.41, 95% CI=0.77, 2.59).

### 5.3.8 Effects of attentional retraining on time to lapse

Figure 29 illustrates the time to first self-reported lapse by trial arm. Censored observations included those who dropped out of treatment and were assumed to have returned to smoking. The median time to lapse was two weeks post-quit in both the AR group (95% CI=0, 8) and control group (95% CI=1, 4). Cox regression analyses revealed that there was no significant difference between trial arms in time to lapse (HR=0.92,  $p=0.71$ , 95% CI=0.57, 1.47).



**Figure 29. Kaplan Meier curve of survival time to first lapse from two weeks prior to quit day to 3 months post-quit**

### **5.3.9 Exploratory analyses of potential moderators of attentional bias**

Linear regression analyses were performed in all cases presented below, with post-training attentional bias score as the outcome variable and trial arm and abstinence status as explanatory variables.

#### **5.3.9.1 Demographic variables**

We investigated whether retraining effects were influenced by demographic variables including participant age at randomisation and gender. These were adjusted for in the analysis of post-training attentional bias scores. The analyses revealed no additional effect of age ( $\beta=0.03$ ,  $p=0.91$ , 95% CI=-0.41, 0.46) or gender ( $\beta=4.62$ ,  $p=0.42$ , 95% CI=-6.78, 16.02) on post-training attentional bias scores.

#### **5.3.9.2 Pre-quit attentional bias**

To assess whether the degree of attentional bias exhibited at baseline had any effect on post-training attentional bias scores, a three-way interaction and two-way interactions between baseline attentional bias score, trial arm and abstinence status were examined. Elimination of all non-significant interactions revealed no additional effect of baseline attentional bias on post-training attentional bias scores. The model indicated a reduction of 0.02 points with a one unit increase in baseline attentional bias score ( $p=0.81$ , 95% CI=-0.20, 0.16).

#### *5.3.9.3 Nicotine dependence*

To examine whether retraining effects were moderated by the severity of nicotine dependence measured at baseline, FTND score was added as a covariate with three-way and two-way interactions between FTND, trial arm and abstinence status. No significant interactions were found ( $p>0.06$ ). The main effect of FTND represented a 0.72 point increase in post-training attentional bias score for every one unit increase in FTND, however this failed to reach statistical significance ( $p=0.56$ , 95% CI=-1.74, 3.18).

#### *5.3.9.4 Pre-quit urge to smoke*

Baseline MPSS-C scores were included as a covariate in the model to determine whether pre-quit urge to smoke predicted post-training attentional bias scores. The analyses revealed no significant main effects or interactions; for every one unit increase in baseline MPSS-C score on a 7-point scale, attentional bias score decreased by 0.29 points ( $p=0.81$ , 95% CI=-2.74, 2.15).

### *5.3.10 Exploratory analyses of potential moderators of urge to smoke*

The most parsimonious model of MPSS-C scores was used in all exploratory analyses reported below.

#### *5.3.10.1 Demographic variables*

Participants' age at randomisation and gender were added as covariates to the model of MPSS-C scores. Neither variable improved the fit of the model ( $\chi^2=0.70$ ,  $p=0.70$ ) and the

coefficients failed to reach statistical significance; there was only a 0.31 point decrease in MPSS-C scores in males compared to females ( $p=0.48$ , 95% CI=-1.16, 0.54) and a 0.02 point decrease in MPSS-C score with every one year increase in age ( $p=0.37$ , 95% CI=-0.05, 0.02).

#### *5.3.10.2 Nicotine dependence*

When FTND score was added as a covariate to the model of MPSS-C scores, no significant three-way or two-way interactions involving FTND, trial arm and abstinence status were found; adding these interaction terms did not significantly improve the fit of the model ( $\chi^2=5.40$ ,  $p=0.25$ ). However, there was a statistically significant main effect of FTND, indicating that for every one unit increase in FTND score, MPSS-C scores increased by 0.22 ( $p=0.02$ , 95% CI=0.03, 0.40).

#### *5.3.10.3 Pre-quit attentional bias*

Baseline attentional bias score was included as a covariate in the parsimonious model of MPSS-C scores to predict the effect of pre-quit attentional bias on urges to smoke over time; three-way and two-way interactions between baseline attentional bias, trial arm and abstinence status were added but the coefficients derived from the model were non-significant ( $ps>0.64$ ). The final model indicated no statistically significant effect of baseline attentional bias score on MPSS-C scores ( $\beta=0.001$ ,  $p=0.79$ , 95% CI=-0.02, 0.01).



### ***5.3.11 Exploratory analyses of potential moderators of withdrawal***

Following the methods used in the exploratory analyses of urge to smoke (section 5.3.10), the most parsimonious model of MPSS-M was used in all exploratory analyses of withdrawal symptoms.

#### ***5.3.11.1 Demographic variables***

Participant age at randomisation and gender were entered as covariates in the model of MPSS-M scores. Neither variable had any additional effect on the model; while the coefficients failed to reach statistical significance, MPSS-M scores increased by 0.37 points in males ( $p=0.75$ , 95% CI=-1.86, 2.60) compared to females and decreased by 0.06 with every one year increase in age ( $p=0.19$ , 95% CI=-0.15, 0.03).

#### ***5.3.11.2 Nicotine dependence***

To examine the effect of nicotine dependence on withdrawal symptoms over time, FTND scores were added to the model of MPSS-M scores. No significant three-way or two way interactions between FTND, trial arm and abstinence status were found and were therefore removed from the model, as there was no improvement in fit ( $\chi^2=2.46$ ,  $p=0.65$ ). The final model indicated that there were no significant effects of FTND scores on MPSS-M scores ( $\beta=0.21$ ,  $p=0.41$ , 95% CI=-0.29, 0.71).

#### *5.3.11.3 Pre-quit attentional bias*

Baseline attentional bias scores were added to the model of MPSS-M scores; no significant three-way or two-way interactions between baseline attentional bias, trial arm and abstinence status were found ( $p>0.63$ ) and were subsequently discarded from the model. The final model revealed that for every one unit increase in bias, MPSS-M scores decreased by 0.02 points, which failed to reach statistical significance ( $p=0.30$ , 95% CI=-0.02, 0.06).

#### *5.3.12 Effects of attentional retraining on cue-induced craving*

##### *5.3.12.1 VAS*

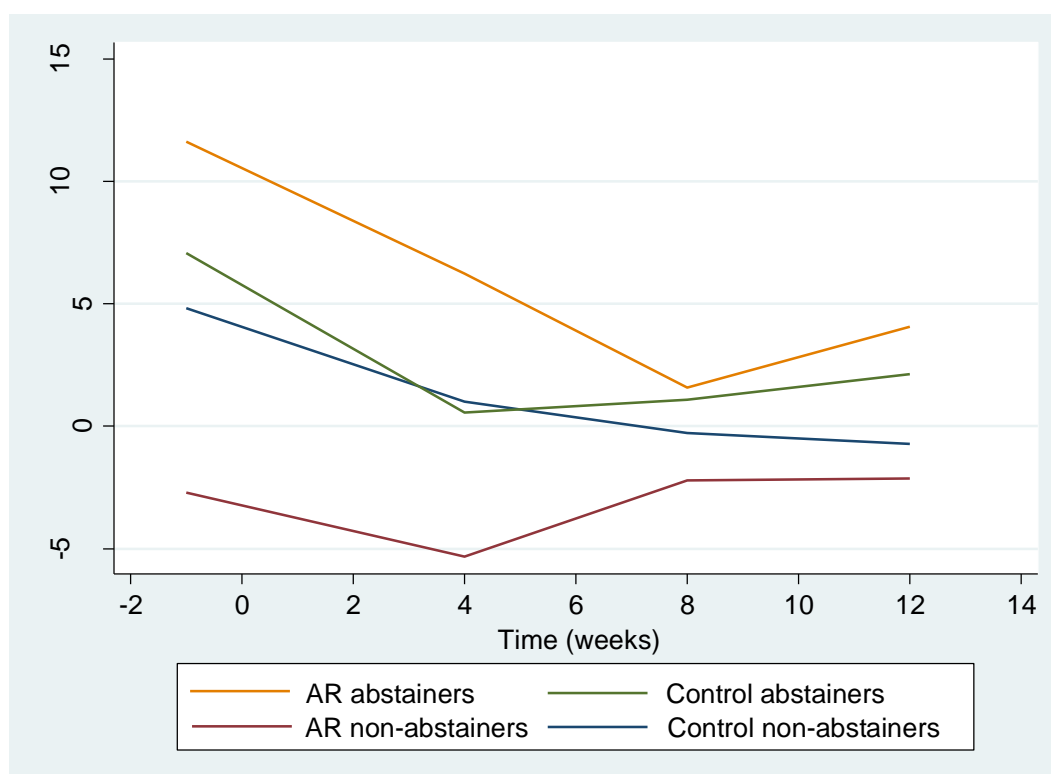
Mean VAS scores for the difference between pre and post cue exposure at baseline, four weeks, eight weeks and three months post-quit by trial arm are shown in Table 21. Across both groups at all time points, VAS craving scores were higher post cue exposure than pre cue exposure. The largest difference in VAS pre and post cue exposure scores was found at pre-training in both groups; thereafter the difference scores were small and similar across groups.

**Table 21. Mean (95%CI) VAS difference scores for craving pre-training and post-training at 4 weeks, 8 weeks and 3 months post-quit by trial arm**

	Attentional retraining (n=58)	Control (n=58)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
VAS difference pre-training	4.47 (24.99)	5.93 (26.78)	-1.46	-0.31	0.76	(-10.94, 8.02)
VAS difference post-training +4 week	1.81 (17.82)	0.74 (11.04)	1.07	0.35	0.73	(-5.05, 7.19)
VAS difference post-training +8 week	0.26 (12.07)	0.60 (11.62)	-0.34	-0.13	0.90	(-5.45, 4.77)
VAS difference post-training 3 months	1.66 (13.89)	0.88 (8.37)	0.78	0.31	0.76	(-4.26, 5.82)

Figure 30 depicts mean VAS difference scores by trial arm and abstinence status.

Abstainers in the AR group had a higher mean difference in VAS craving pre and post cue exposure than the control group across all time points. The mean difference in VAS craving scores among non-abstainers was generally lower than that found in abstainers across both groups.

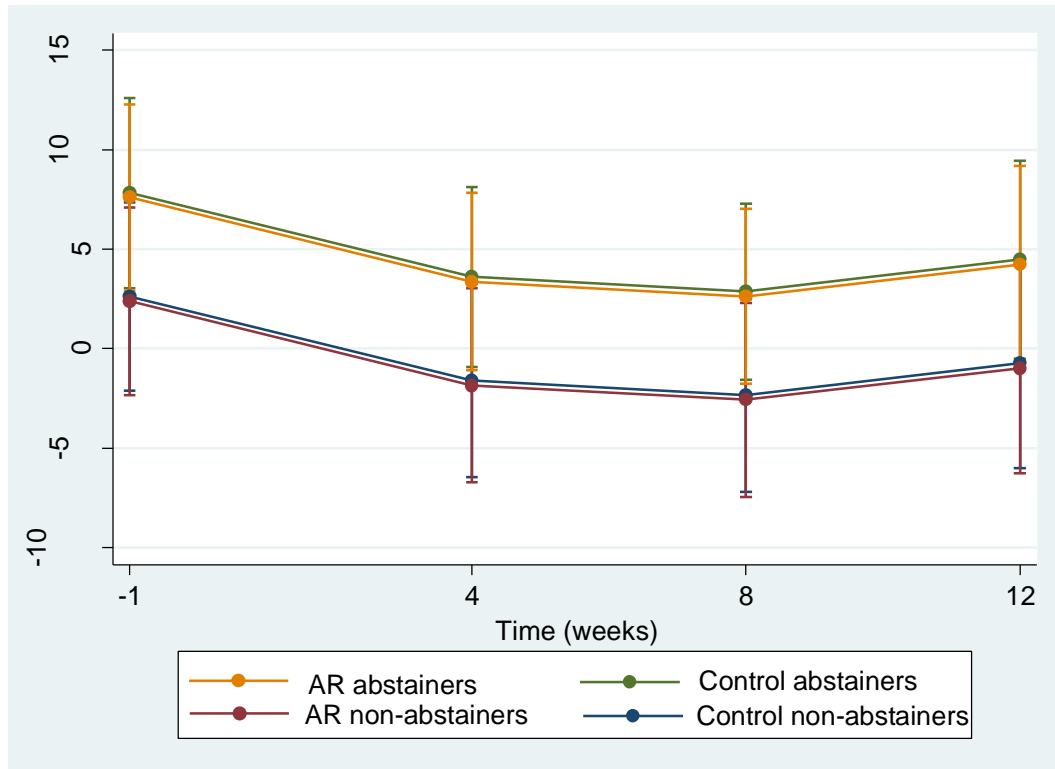


**Figure 30. Mean VAS difference scores by trial arm and abstinence status from quit day to 3 months (n=116)**

The fully specified mixed-effects model of VAS difference scores did not contain any significant three-way or two-way interactions between trial arm, abstinence status and time (Appendix 31); following backward elimination of all non-significant interactions, only the main effects of trial arm, abstinence status and time remained in the model. Model comparisons indicated no significant loss in the log-likelihood between the fully specified model and the parsimonious model ( $\chi^2=3.54$ ,  $p=0.83$ ).

Linear combinations of the coefficients from the parsimonious model indicated a small non-significant 0.22 point reduction in VAS craving difference scores in the AR group compared to the control group ( $p=0.93$ , 95% CI=-5.06, 4.60; Figure 31). The comparison

by abstinence status revealed that VAS difference scores were significantly higher in abstainers than non-abstainers ( $\beta=5.21$ ,  $p=0.04$ , 95% CI=0.32, 10.10).



**Figure 31. Predicted VAS difference scores for craving (95% CI) by trial arm and abstinence status from one week prior to quit day to 3 months post-quit**

### 5.3.13 Other cognitive processing bias measures

#### 5.3.13.1 Baseline Stroop bias

Participants across the sample did respond in the predicted direction and were slower to colour-name smoking-related pictures than neutral pictures (mean difference=4.87).

However, a one-sample t-test against zero indicated that this difference was not significant at baseline ( $t[117]=0.87$ ,  $p=0.39$ ).

### 5.3.13.2 Effects of attentional retraining on pictorial Stroop bias

Mean Stroop bias RT scores by trial arm are shown in Table 22. A one-way between groups ANCOVA adjusted for pre-training Stroop bias scores was performed to assess group differences in Stroop bias at four weeks post-quit. No significant differences were found between groups in post-training Stroop bias scores ( $F[2,85]=0.25$ ,  $p=0.62$ ).

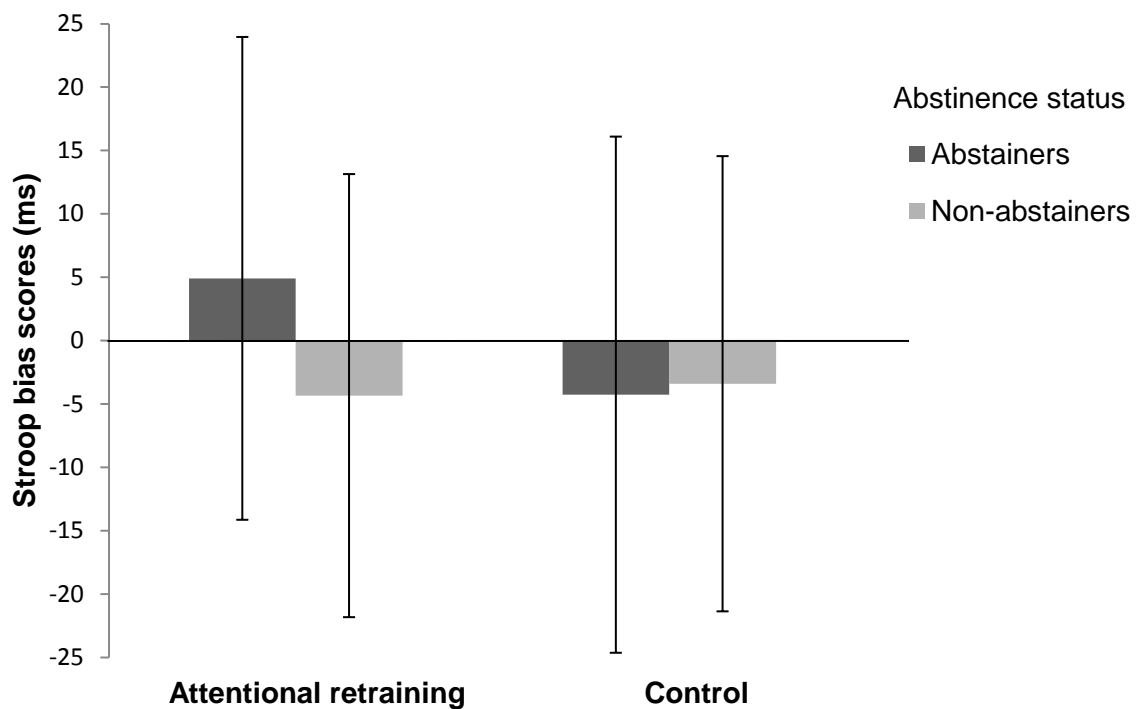
Similarly, when a 2 x 2 between-groups ANCOVA was performed with abstinence status included, there were no significant main effects or interactions ( $F_s < 0.22$ ,  $p_s > 0.67$ ).

**Table 22. Pre-training and post-training Stroop bias scores at 4 weeks, 8 weeks and 3 months by trial arm**

	Attentional retraining (n=60)	Control (n=58)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	834.18 (154.70)	801.36 (131.75)	32.81	1.24	0.22	(-19.66, 85.29)
RT for neutral stimuli	824.28 (160.09)	801.70 (129.31)	22.58	0.84	0.40	(-30.59, 75.75)
Attentional bias	9.90 (62.85)	-0.34 (59.07)	10.24	0.91	0.36	(-12.02, 32.49)
Post-training +4 week						
RT for smoking stimuli	838.78 (133.46)	792.64 (148.86)	40.56	1.53	0.13	(-13.69, 105.97)
RT for neutral stimuli	837.34 (144.91)	796.77 (148.39)	46.14	1.30	0.20	(-21.62, 102.75)
Attentional bias	1.45 (55.13)	-4.13 (39.96)	5.58	0.55	0.59	(-14.72, 25.87)
Post-training +8 week						
RT for smoking stimuli	828.30 (145.87)	807.18 (148.40)	21.11	0.66	0.51	(-42.39, 84.62)
RT for neutral stimuli	830.97 (150.90)	822.55 (143.45)	8.42	0.26	0.79	(-55.20, 72.04)
Attentional bias	-2.67 (45.09)	-15.37 (64.44)	12.70	1.06	0.29	(-11.17, 36.56)
Post-training 3 months						
RT for smoking stimuli	838.52 (129.66)	810.33 (148.92)	28.20	0.92	0.36	(-33.08, 89.48)
RT for neutral stimuli	834.04 (139.65)	793.86 (138.86)	40.17	1.31	0.20	(-21.06, 101.40)
Attentional bias	4.49 (58.60)	16.46 (63.19)	-11.97	-0.89	0.38	(-38.74, 14.79)

*RT - reaction time (milliseconds)*

Among abstainers only, Stroop bias scores were higher in the AR group than the control group post-training ( $\beta=9.18$ ,  $p=0.50$ , 95% CI=-17.47, 35.83), while in non-abstainers, bias scores were 0.94 points less in the AR group compared to the control group ( $p=0.96$ , 95% CI=-34.86, 32.98; see Figure 32).



**Figure 32. Stroop bias scores (ms) with 95% CI by abstinence status in the attentional retraining group (n=60) and control group (n=58)**

#### 5.3.13.3 Effects of attentional retraining on pictorial Stroop bias – imputed dataset

The ANCOVA reported in section 5.3.13.2 was re-run using imputed Stroop RT scores for missing values; however there was no significant difference in Stroop bias scores at four weeks post-quit between trial arms ( $F[2,93]=0.06$ ,  $p=0.80$ ) or with abstinence status added as an additional variable and interaction ( $F[4,91]=0.26$ ,  $p=0.62$ ).

#### **5.3.14    *Effects of attentional retraining on trained ‘old’ stimuli on the visual probe task***

Mean RT scores for attentional bias on trained stimuli only are presented in Table 23. To examine attentional retraining effects on trained stimuli only, a one-way between groups ANCOVA adjusted for pre-training attentional bias scores was performed on the stimuli that were used during training sessions only. This was initially carried out with the inclusion of trial arm, followed by an interaction with abstinence status. The ANCOVA revealed no significant differences between groups ( $F[2,81]=0.16$ ,  $p=0.85$ ) or by abstinence status ( $F[4,79]=0.40$ ,  $p=0.81$ ).

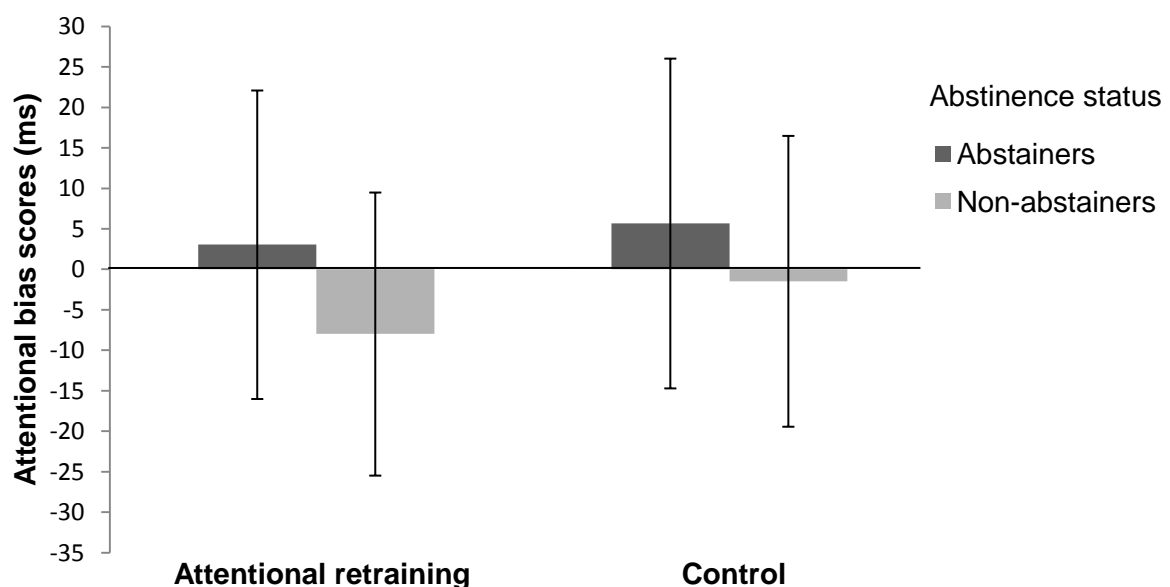
In analyses of abstainers only, attentional bias scores were 2.62 points lower in the AR group compared to the control group for trained stimuli, although this failed to reach statistical significance ( $p=0.80$ , 95% CI=-23.15, 17.90). Across non-abstainers only, the difference was larger in the AR group compared to the control group but again, the size of this effect was small and did not reach statistical significance ( $\beta=-6.52$ ,  $p=0.62$ , 95% CI=-32.24, 19.21; Figure 33).



**Table 23. Pre-training and post-training attentional bias scores for trained stimuli only at 4 weeks, 8 weeks and 3 months by trial arm**

	Attentional retraining (n=58)	Control (n=58)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	684.52 (156.11)	680.40 (139.19)	4.12	0.15	0.88	(-50.28, 58.52)
RT for neutral stimuli	668.30 (199.91)	686.63 (139.88)	-18.32	-0.58	0.57	(-81.43, 44.79)
Attentional bias	6.84 (27.50)	6.23 (47.59)	0.60	0.08	0.93	(-13.69, 14.90)
Post-training +4 week						
RT for smoking stimuli	681.96 (132.69)	651.81 (139.61)	30.14	1.03	0.31	(-28.30, 88.59)
RT for neutral stimuli	680.68 (129.51)	654.82 (142.83)	25.86	0.88	0.38	(-32.54, 84.27)
Attentional bias	-1.27 (35.00)	3.01 (37.13)	-4.28	-0.55	0.58	(-19.76, 11.20)
Post-training +8 week						
RT for smoking stimuli	670.09 (125.25)	649.50 (117.71)	20.59	0.79	0.48	(-30.97, 72.15)
RT for neutral stimuli	669.27 (121.70)	648.02 (115.96)	21.24	0.84	0.77	(-29.18, 71.66)
Attentional bias	-0.82 (35.59)	-1.48 (35.09)	0.65	0.09	0.42	(-14.33, 15.64)
Post-training 3 months						
RT for smoking stimuli	681.42 (159.52)	664.85 (135.85)	16.57	0.51	0.62	(-48.70, 81.84)
RT for neutral stimuli	686.46 (157.51)	668.40 (139.48)	18.06	0.55	0.59	(-47.44, 83.57)
Attentional bias	5.05 (35.14)	3.55 (29.37)	1.50	0.21	0.84	(-12.77, 15.77)

RT - reaction time (milliseconds)

**Figure 33. Attentional bias scores (ms) for trained stimuli only with 95% CI by abstinence status in the attentional retraining group (n=58) and control group (n=58)**

### ***5.3.15 Effects of attentional retraining on untrained ‘novel’ stimuli on the visual probe task***

Mean RT scores for attentional bias on untrained stimuli only are presented in Table 24.

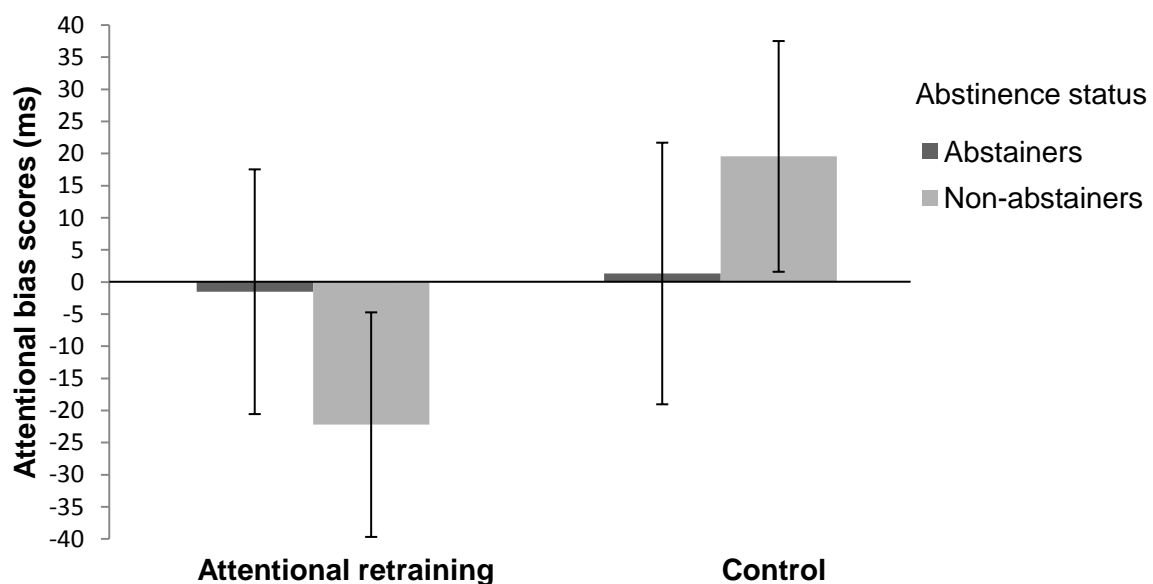
We examined retraining effects on untrained stimuli only in a one-way between groups ANCOVA adjusted for pre-training attentional bias scores. The ANCOVA revealed no significant differences between groups ( $F[2,81]=2.26$ ,  $p=0.11$ ) but a significant effect was found when abstinence status was included with an interaction with trial arm ( $F[4,79]=2.51$ ,  $p=0.05$ ).

Across abstainers only, attentional bias scores were 2.84 points lower post-training in the AR group compared to the control group, although this was not statistically significant ( $p=0.79$ , 95% CI=-23.81, 18.13). On the other hand in non-abstainers, attentional bias scores were significantly lower by 41.76 points in the AR group than the control group ( $p=0.002$ , 95% CI=-68.34, -15.18; Figure 34).

**Table 24. Pre-training and post-training attentional bias scores for untrained stimuli only at 4 weeks, 8 weeks and 3 months by trial arm**

	Attentional retraining (n=58)	Control (n=58)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	686.83 (154.97)	690.22 (124.51)	-3.39	-0.13	0.90	(-55.10, 48.32)
RT for neutral stimuli	659.22 (201.89)	694.04 (132.41)	-34.83	-1.10	0.27	(-97.30, 27.65)
Attentional bias	-4.88 (33.09)	3.83 (38.45)	-8.71	-1.31	0.19	(-21.90, 4.49)
Post-training +4 week						
RT for smoking stimuli	694.65 (134.84)	655.91 (136.04)	38.74	1.32	0.61	(-19.47, 96.95)
RT for neutral stimuli	686.21 (122.65)	663.44 (146.65)	22.77	0.78	0.32	(-34.98, 80.52)
Attentional bias	-8.45 (38.64)	7.53 (37.04)	-15.97	-1.95	0.42	(-32.27, 0.32)
Post-training +8 week						
RT for smoking stimuli	675.57 (137.62)	666.50 (124.37)	9.07	0.32	0.75	(-46.60, 64.74)
RT for neutral stimuli	676.84 (130.75)	653.76 (118.33)	23.09	0.87	0.39	(-29.83, 76.01)
Attentional bias	1.28 (35.00)	-12.74 (38.62)	14.02	1.79	0.08	(-1.58, 29.63)
Post-training 3 months						
RT for smoking stimuli	684.51 (151.78)	674.58 (142.37)	9.94	0.31	0.76	(-54.81, 74.68)
RT for neutral stimuli	680.42 (157.66)	669.19 (136.44)	11.23	0.72	0.73	(-53.71, 76.16)
Attentional bias	-4.10 (50.19)	-5.39 (45.70)	1.29	0.85	0.90	(-19.84, 22.42)

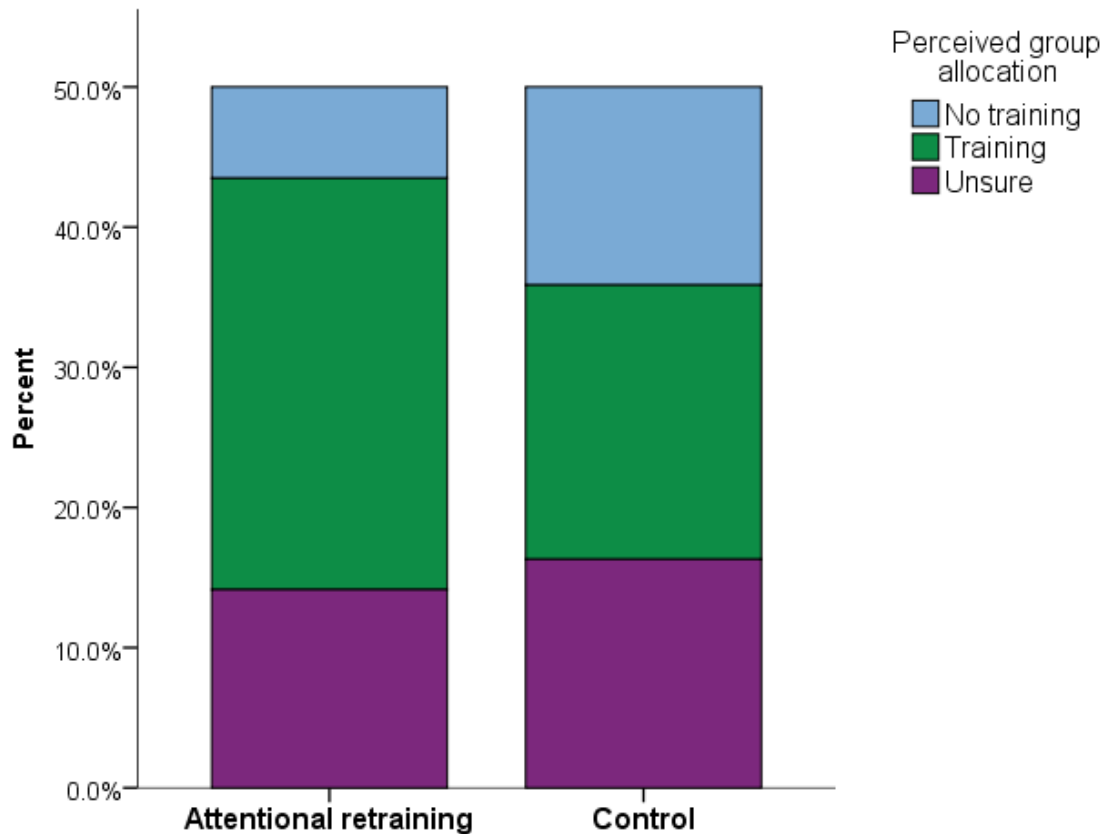
RT - reaction time (milliseconds)

**Figure 34. Attentional bias scores (ms) for untrained stimuli only with 95% CI by abstinence status in the attentional retraining group (n=58) and control group (n=58)**

### ***5.3.16 Identification of group allocation***

Self-reported data on group allocation were missing from two participants at follow up, excluding those who had dropped out of the study and were lost-to-follow up after randomisation. Data were therefore available for 92 participants. Figure 35 illustrates participant responses as a percentage within each group. Most participants in the AR group correctly identified that they had received training (58.7%). In the control group, the majority of participants incorrectly identified that they had received training or were unsure of their allocation (71.7%).

Kappa was used to measure the degree of agreement between the number of correct responses to group allocation and actual allocation; overall there was marginal agreement (Kappa=0.13,  $p=0.03$ ).



**Figure 35. Self-reported responses (%) to group allocation by trial arm (n=92)**

### ***5.3.17 Observational analysis: association between attentional bias, craving and withdrawal symptoms at baseline***

To examine whether the visual probe task measure of attentional bias correlated with craving and withdrawal measures at baseline, Pearson's correlations were performed between baseline attentional bias scores, MPSS-C scores, MPSS-M scores and VAS score for the item "craving a cigarette" on all participants. There was a positive correlation between MPSS-C and VAS craving measures ( $r=+0.23$ ,  $p<0.05$ ) and between MPSS-C and MPSS-M scores ( $r=+0.40$ ,  $p<0.001$ ), but none of these measures correlated with attentional bias scores ( $ps>0.77$ ).

### ***5.3.18 Observational analysis: attentional bias associations with measures of dependence and clinical outcomes***

To facilitate interpretation of the coefficients derived from the linear regression analyses presented below, the coefficients were multiplied by 100.

#### ***5.3.18.1 Associations with nicotine dependence***

There were no significant associations between attentional bias measured by the visual probe task or Stroop task and markers of dependence. On the visual probe task measure, FTND decreased by 0.20 ( $p=0.77$ , 95% CI=-1.60, 1.19) and cigarettes per day decreased by 4 ( $p=0.17$ , 95% CI=-9.74, 1.70) with every 100 unit increase in bias score. On the Stroop task measure, FTND decreased by 0.02 ( $p=0.95$ , 95% CI=-0.66, 0.71) and cigarettes per day decreased by 1 ( $p=0.47$ , 95% CI=-1.77, 3.79) with every 100 unit increase in bias score.

#### ***5.3.18.2 Associations with urge to smoke***

There were no significant associations between attentional bias measured by the visual probe task or Stroop task and urge to smoke. A mixed-effects model of MPSS-C scores with an interaction between attentional bias and period of quit attempt (to delineate pre-quit from post-quit) indicated no significant main effects or interactions ( $p>0.41$ ). We found a 0.30 point non-significant increase in MPSS-C with every 100 unit increase in bias score ( $p=0.59$ , 95% CI=-0.98, 1.74). Similarly, using the Stroop task measure in a

mixed-effects model of MPSS-C scores, there was a 0.50 point non-significant increase in MPSS-C with every 100 unit increase in bias score ( $p=0.12$ , 95% CI=-0.13, 1.18).

#### *5.3.18.3 Associations with withdrawal symptoms*

There were no significant associations between attentional bias measured by the visual probe task or Stroop task and severity of withdrawal mood symptoms. Similar to the analysis of MPSS-C scores in section 5.3.18.2, a mixed-effects model of MPSS-M scores indicated a 2.22 point non-significant reduction in pre-quit withdrawal symptoms with every 100 unit increase in bias scores ( $p=0.22$ , 95% CI=-5.77, 1.33). On the Stroop task, there was a 0.38 point non-significant increase in MPSS-M with every 100 unit increase in bias scores ( $p=0.66$ , 95% CI=-1.31, 2.07).

#### *5.3.18.4 Association with smoking abstinence at 4 weeks*

Over all participants, neither the visual probe task measure of attentional bias taken at baseline (OR=0.79, 95% CI=0.23, 2.74) nor Stroop bias measure (OR=1.15, 95% CI=0.63, 2.10) predicted four weeks abstinence.

## **5.4 Discussion**

### *5.4.1 Summary of principal findings*

This study examined the efficacy of AR on attentional bias and smoking cessation outcomes in smokers attempting to stop smoking. The overall finding suggested that there

was no statistically significant effect of retraining on attentional bias, urge to smoke, withdrawal symptoms or abstinence rates in the AR group compared to the control group.

There was no association between baseline attentional bias scores and baseline craving, although both MPSS-C and VAS craving measures correlated with each other. Similarly there was no association between baseline attentional bias scores and withdrawal scores, but one measure of craving (MPSS-C) correlated with withdrawal scores.

Abstainers in the AR group had lower attentional bias scores post-training than those in the control group, but this was not statistically significant and the effect size was too small to be clinically meaningful. No significant differences in attentional bias scores were found between groups at follow-up. There was a non-significant reduction in MPSS-C scores among abstainers in the AR group compared to the control group but again, these effects were negligible. This reduction was maintained at follow-up in abstainers. There was no difference between groups in withdrawal symptom profiles, although the AR group exhibited a non-significant increase in withdrawal over time, which was also observed at the follow-up time points.

Abstinence rates were similar across both groups, indicating that AR had no effect on quitting. Moreover, the groups did not differ in time to first lapse.



We observed no retraining effects on cue-induced craving; the difference between pre and post cue exposure task ratings at each follow-up was only marginally smaller in the AR group compared to the control group. Overall, the difference in craving scores pre and post cue exposure was higher in abstainers than non-abstainers.

Attentional retraining did not generalize to other measures of cognitive bias (the pictorial Stroop task) or to untrained ‘novel’ stimuli among abstainers on the visual probe task, although non-abstainers did show reductions in attentional bias.

As found in current smokers in the earlier study, this sample of treatment-seekers did not exhibit an attentional bias at baseline. Moreover, retraining effects were not moderated by baseline attentional bias, i.e. the degree of attentional bias exhibited at baseline had no impact on post-training attentional bias scores, craving and withdrawal symptoms.

Similarly, age, gender, FTND and pre-quit urge to smoke had little impact as potential moderators, although severity of nicotine dependence was moderately associated with urge to smoke and to a lesser degree, with attentional bias.

Irrespective of retraining, neither attentional bias measure showed reliable associations with nicotine dependence nor any of the clinical outcomes measured in the study. The implications of these observational findings in relation to the trial results are discussed later in section 5.4.2.

### ***5.4.2 The findings in the context of previous studies***

This study provides partial support for other tobacco-related retraining studies (Field et al., 2009b; McHugh et al., 2010) but not the Attwood et al. (2008) study. Attwood et al. (2008) found that attentional retraining significantly reduced attentional bias in their train-to-avoid group, while in Field et al. (2009b), the reduction in bias only approached statistical significance.

Crucially, both Attwood et al. (2008) and Field et al. (2009b) demonstrated that the current smokers in their studies exhibited an attentional bias at baseline, while participants in our study did not. Our findings therefore concur mostly with our earlier study (Chapter 2) and McHugh et al. (2010), who found no attentional bias in their sample at baseline and no attentional retraining effects in those trained to avoid smoking cues. Of particular note is that attentional bias was normally distributed in our sample, with a large number of participants failing to show a bias towards smoking cues; in fact some showed a negative bias at baseline. This finding is perhaps more indicative of attentional bias in real-world settings with treatment-seeking populations, which is a departure from the unrepresentative samples typically recruited in the laboratory studies mentioned above. The implications of this are described in more detail in section 5.4.4.

Arguably, the studies by Waters et al. (2003a, 2003c) are most relevant to the discussion of attentional bias in clinical populations. The first of these studies measured selective processing biases on the Stroop task while the second study used the visual probe task, both of which assessed smokers attempting to quit on nicotine patches or placebo patches.

Smokers across both studies showed a significant attentional bias towards smoking cues [64 ms bias in Waters et al. (2003a) and 3 ms bias in Waters et al. (2003c)]. A key difference in the design of the first study is that selective processing biases were measured on the first day of abstinence, unlike in Waters et al. (2003c) and this study where participants – though treatment seekers – were assessed in a non-deprived state. Across a handful of previous studies, participants have typically observed a period of abstinence prior to testing, e.g. for at least one hour in laboratory studies (Field et al., 2009b) or overnight in clinical studies (Powell et al., 2010). Indeed some investigators have found that nicotine deprivation level affects attentional bias (Field et al., 2004; Freeman et al., 2012), whilst others have not (Canamar & London, 2012; Mogg & Bradley, 2002). For example, Field et al. (2004) assessed nicotine deprived and non-deprived smokers' eye movements during a visual probe task and found that while both groups exhibited an attentional orienting towards smoking cues, deprivation increased the maintenance of gaze on smoking cues than neutral cues compared to those who were satiated. Although deprivation level did not appear to significantly affect bias on other measures in the Field et al. (2004) study, i.e. the direction of initial eye movement or visual probe task RTs at a stimulus duration of 2000 ms, a recent study demonstrated that abstinent smokers had faster RTs towards smoking cues than neutral cues compared to satiated smokers and non-smoker controls on a visual probe task that employed a shorter stimulus duration of 250 ms (Freeman et al., 2012). Aside from the need to clarify which measures are most sensitive to the measurement of attentional bias and the effects of nicotine deprivation, future investigations should consider the potential impact of deprivation state on attentional bias when measured in treatment-seeking populations.

While it may have been more difficult to detect retraining effects in a sample that did not show a significant attentional bias in the first instance, we also found that AR had little impact in those that did show a bias. It would seem that delivering AR in those identified with an a priori bias may still be insufficient to produce the desired change in attentional bias and smoking cessation outcomes.

Attentional retraining had no apparent effects on urge to smoke, cue-induced craving and withdrawal symptoms. The lack of effect is consistent with findings of the earlier laboratory study and other tobacco and alcohol-related studies with a train-to-avoid manipulation (Field et al., 2009b; McHugh et al., 2010; Schoenmakers et al., 2007). Although there was some indication of a reduction in urge to smoke over time in abstainers in the AR group compared to the control group, the effects were negligible. The causal association between attentional bias and craving has been described as weak at best particularly in tobacco studies (Field et al., 2009a) and so these small effects are unsurprising. Previous retraining studies have only lent support for this causal association in one direction of change, i.e. by demonstrating that increases in attentional bias are associated with increases in urge to smoke (Attwood et al., 2008) or urge to drink (Field & Eastwood, 2005); however, most retraining studies have failed to demonstrate that decreases in attentional bias reduce craving across non-treatment seeking populations (Field et al., 2009b; McHugh et al., 2010) and critically, in clinical populations (Schoenmakers et al., 2010). Taken together, this study is the first to illustrate that attentional retraining on the visual probe task did not have a reliable effect on craving or withdrawal symptoms in treatment-seeking smokers.

Additionally, this was the first study to demonstrate that AR had no effect on time to first lapse and relapse to smoking. Comparatively, alcohol retraining studies in clinical populations have found tentative evidence of retraining effects on clinical outcomes, e.g. Fadardi and Cox (2009) demonstrated that harmful drinkers reduced their weekly alcohol consumption over four sessions of being trained away from alcohol cues, with reductions maintained up to three months after the first session. Similarly, Schoenmakers et al. (2010) found that alcohol-dependent patients in a train-to-avoid group were discharged from treatment earlier and remained abstinent for longer in comparison to a control group. That said, it is worth noting that the lack of effects found on the behavioural outcomes in this study should be interpreted with some caution as this study was not powered to detect differences in abstinence.

There are several issues relating to the procedural aspects of this study that are relevant to consider in the context of previous AR studies. Primarily, most attentional retraining protocols assess the effects of training immediately after the session in which it was delivered (Attwood et al., 2008; Field & Eastwood, 2005; Schoenmakers et al., 2007). In this study, to minimize participant burden, the first follow-up attentional bias assessment was carried out at least one week after the last training session. This time lag between training and assessment may have attenuated any immediate effects of retraining that might have occurred. That said, if attentional bias plays a role in the maintenance of addiction, the aim would be to observe global changes in attentional bias and not momentary changes and so any retraining effects would need to be maintained in the long-term. Our findings concur with those of Field et al. (2009b); although the authors found differential retraining effects by group immediately after training, these effects

dissipated the day after. Indeed, we found no evidence of group differences in attentional bias at any of the follow up assessments, and so we were unable to establish whether retraining effects were stable over time.

Given the evident time lag between training and assessment, we might also question whether it was sufficient to deliver the training in weekly sessions. There is no evidence to date to inform the optimum number or regularity of training sessions in addiction-related attentional retraining protocols. Daily sessions may be more efficacious although there are practical difficulties in delivering these within existing NHS stop smoking clinics, which follow a pattern of weekly visits as part of usual care. On the one hand, web-based training could be an alternative delivery system as patients could access the training program more readily from a remote location, for example, if they had a computer at home; however this method of delivering AR has yet to show efficacy in the treatment of social anxiety disorders, with most studies (Carlbring et al., 2012; Neubauer et al., 2013) failing to replicate the anxiety symptom reductions found in clinic-delivered sessions (Schmidt et al., 2009). The use of mobile technology appears to be a more promising way of delivering training (Kerst & Waters, 2013), which I discuss later in section 5.4.4.

Like the number of training sessions, it is unclear whether enough training trials and picture pairs were used to produce the desired learning effect. To minimize effects of participant boredom, we limited the training to 192 trials per session, which was a significant departure from what has been used in previous tobacco-related retraining

studies; for example, Attwood et al. (2008) used 512 trials while Field et al. (2009b) used 896 trials. In light of these comparisons, the use of fewer training trials could have compromised the effectiveness of training. In other psychopathologies however, multiple sessions of training consisting of 160 trials have been sufficient to reduce attentional bias and symptoms of social anxiety (Amir et al., 2009b; Schmidt et al., 2009). Comparisons made between other domains and addiction should be interpreted with caution though, because the mechanism of AR is likely to differ, as the neural pathways underlying attentional bias are thought to be different (Wiers & Stacy, 2006).

We found that generalization of the learning effect may have occurred in non-abstainers in the AR group – but not in abstainers – as demonstrated by a reduction in bias towards stimuli that were not used during the training sessions. This could indicate that the number of picture pairs used was sufficient enough to produce a global effect rather than a stimuli-specific retraining effect on attentional bias. This effect has not been observed before in tobacco studies (Field et al., 2009b) but has been found in one alcohol study (Schoenmakers et al., 2010), but not others (Field et al., 2007b; Schoenmakers et al., 2007). It is unclear why we found differential retraining effects for novel stimuli by abstinence status but we could consider that individual differences within subjects may have contributed to this effect. We should be cautious in our interpretation of the generalizability of training because this result was only found in sub-group analyses and the effect disappeared in the analysis by treatment group only, when the sample size was larger. Furthermore, the findings must be qualified because participants did not show retraining effects in response to stimuli that were used during the training sessions. If

there are retraining effects, a failure to observe a reliable reduction in attentional bias across all assessment stimuli indicates a lack of consistency in any effect.

The finding that AR did not generalize to other task procedures is in line with previous studies (Field et al., 2007b; Field et al., 2009b; Schoenmakers et al., 2007). Correlations between attentional bias tasks are generally poor and may reflect the fact that different tasks measure different aspects of attentional processing (Mogg & Bradley, 2002). Thus, retraining on one task may not tap into the mechanism underlying attentional processing in another task. However, as participants did not show an attentional bias prior to training on the visual probe task or the pictorial Stroop task, generalization of any possible retraining effects are difficult to interpret in this study.

I have thus far described how AR did not work as a preventative treatment for relapse in this study and discussed protocol design issues around why this might have been the case. The finding that attentional bias was not associated with indices of dependence, urge to smoke, withdrawal symptoms or relapse to smoking on neither task measure warrants consideration too. One interpretation may indeed be that smoking-related attentional bias is not an important phenomenon in the quitting process and therefore an unworthy target for intervention. However, this would go against much of the existing evidence reviewed in Chapter 1 on the value of attentional processing in addictive behaviours [see Field & Cox (2008) for a comprehensive review] and anecdotal evidence from drug users themselves who reflect on the ability of drug cues to capture their attention. What remains clear is that correlations between these constructs are often weak and that experimental



manipulation of one process does not always lead to a corresponding change in another. Instead we might consider that some processes like attentional bias and craving could have an altogether independent influence on smoking behaviour.

Another plausible explanation for the lack of associations found could be because the task measures used in this study were not sensitive enough to assess attentional processing and any potential changes in bias. Coupled with the finding that the sample did not show a marked attentional bias at baseline, we are led to question whether indirect measures of cognitive bias like the visual probe task and Stroop task reliably and consistently tap into these processes. Lending weight to this explanation, Ataya et al. (2012a) conducted a study on the psychometric properties of visual probe and Stroop task measures of cognitive bias. The authors report on seven independent laboratory studies and concluded that both tasks showed poor internal reliability, particularly the visual probe task which had a smaller Cronbach's alpha coefficient than the Stroop task ( $\alpha=0.18$  vs  $\alpha=0.74$ , respectively) which was considered against a minimum accepted standard of 0.70 (Kline, 1999).

In response to this paper, Field and Christiansen (2012) argue that more direct measures of attention using eye-tracking methodology for example, may be more reliable than reaction time indices; their examination of one of their own studies on cannabis users (Field et al., 2006) indicated that the internal reliability of an eye-movement monitoring task was superior to that of a visual probe task delivered in parallel ( $\alpha=0.71$  vs  $\alpha=0.53$ , respectively). Indeed the association between attentional bias and subjective craving has

been noted as larger for direct measures than indirect measures of bias [ $r=0.36$  vs  $r=0.18$ , respectively, see Field et al. (2009a)], further supporting the notion that direct measures may be more sensitive to indexing attentional bias than indirect measures.

A second observation by Field and Christiansen (2012) is that participants may vary in the degree of responsiveness to particular stimuli used within each task, based on whether these stimuli bear any relevance to the individual. Some stimuli may therefore induce more bias than others; however when reaction time scores are averaged across all trials, the resultant bias may be small (Field & Christiansen, 2012). However, as Ataya et al. (2012b) allude to, it may be somewhat cumbersome and difficult to implement a tailored approach to stimulus selection, given the numerous factors that are likely to influence the salience of a cue, e.g. real-world contextual factors are not readily captured in stimuli used across existing studies. That said, investigators have now moved forward to identify more ecologically valid stimulus sets capable of evoking heightened motivational responses (Conklin et al., 2008; Conklin et al., 2010). For example, Conklin et al. (2010) had participants take pictures of their real-world smoking and non-smoking environments and compare them to generic environments in a cue exposure session. The difference in self-reported craving was larger for personalised stimuli than standard stimuli. However, personalisation of stimuli has not always produced greater attentional bias in other addictions. For example, Fridrici et al. (2013) found that alcohol-dependent patients neither showed a processing bias towards alcohol-related on a Stroop task nor showed increased interference for individualised alcohol-related words compared to generic alcohol-related words. Personalised pictorial stimuli may produce different results, and so

future investigations should still consider this as a potential way of increasing the reliability of cognitive bias measures.

#### ***5.4.3 Strengths and limitations of the ARTS trial***

One of the strengths of this study is that it was the first translational study to examine the effects of tobacco-related attentional retraining in a clinical population. Prior investigations have only focused on non treatment-seeking smokers (Attwood et al., 2008; Field et al., 2009b; McHugh et al., 2010); the utility of AR procedures is most appropriate to assess in those wanting to modify their behaviour. Secondly, this was the first study to assess the effects of multiple sessions of AR in smokers attempting to quit, as other studies only report on carrying out a single session [apart from the study by Kerst & Waters (2013) but the sample were current smokers].

There are several limitations to consider. To avoid unblinding, we did not assess whether participants were aware of the training contingencies, i.e., if they could correctly identify a relationship between the location of the probe and picture type during the training sessions. Both cognitive bias tasks and ratings of craving and withdrawal could be susceptible to demand effects and so this was not assessed during the study. Previous AR studies that typically train and assess participants within a single session often ask participants about the training contingencies at the end of the session. As the last follow-up session was approximately five months from the last training session, we considered that participants would not have been able to accurately recall if there was a relationship between the probe location and picture type, especially as they would have been

accustomed to the assessment version. We did, however, ask participants which group they thought they had been randomised to; mixed responses across both groups suggest no true knowledge of group allocation, with many participants stating that they had guessed their allocation. There is tentative evidence that retraining effects are mediated by contingency awareness; for example, increases in craving have been found in train-to-attend groups only in those who were aware of being trained towards their drug of choice (Attwood et al., 2008; Field et al., 2007b). Many of the studies that have shown successful reductions in attentional bias and improvements in clinical outcomes have informed their participants of the principle behind training (Fadardi & Cox, 2009; Schoenmakers et al., 2010). Awareness might increase engagement with the task too. Future studies that manipulate whether participants are contingency aware or not may shed light on the necessity of awareness and clarify the mechanisms that may underlie retraining effects.

Another limitation of the study is that we did not control for or assess time since last cigarette at baseline. This may partly explain why we did not observe an attentional bias in the sample at baseline. It is possible that participants were satiated at the time of assessments, and as I have discussed in section 5.4.2, nicotine satiation may reduce or eliminate attentional bias and ratings of craving and withdrawal. Similarly, for those that lapsed between clinic sessions, we do not know how close to a training session a cigarette was smoked. We might speculate that if a positive association between attentional bias and craving exists (Field et al., 2009a) and attentional bias is somewhat mediated by nicotine deprivation level (Field et al., 2004), attentional bias and craving would be lower immediately after smoking. This would hypothetically reduce the likelihood of observing retraining effects if training was delivered immediately after a lapse occurred. That said,

the overall effect of AR on attentional bias appeared to be larger in non-abstainers than abstainers in the AR group compared to the control group, which perhaps undermines this argument.

Finally, we did not record the actual day in which a lapse occurred and so the time to first lapse analysis may be somewhat inaccurate. Evidence indicates that lapses and relapse to smoking occur most commonly within the first eight days of a quit attempt (Hughes et al., 2004a). Lapses in this study were reported by participants during weekly clinic visits, only to verify whether a lapse had occurred or not in the preceding week. Timeline follow-back procedures (TLFB) whereby participants use a calendar to indicate when a lapse occurred may have given a more accurate timing of lapse date (Brown et al., 1998), yet this method also has its own limitations by relying on participants to recall lapse days from memory. Again, EMA methods may obviate recall bias as lapses can be recorded as they happen, but these methods are only worthwhile if participants adhere to EMA protocols.

#### ***5.4.4 Implications of the ARTS trial findings***

Based on the findings of this study, we are unable to advocate the use of AR procedures as a preventative treatment for relapse to smoking. The clinical value of such procedures for smoking cessation is limited, based on the lack of any consistent effects found and the confidence intervals exclude moderate sized effects. Until the measures for assessing attentional bias are validated and the design of the intervention is improved, it may be some time before we are able to ascertain the true potential of AR as a clinical tool.

In a broader sense, we are led to question whether laboratory methods are capable of addressing complex real-world processes (Ataya et al., 2012b). While the task measures used in these studies may require refinement, the population groups in which these measures are tested in may need consideration too. In the real-world, there is considerable variation in psychological, motivational and behavioural processes across populations (Henrich et al., 2010). However, laboratory studies typically recruit highly unrepresentative samples, often consisting of university students paid to take part in research. Indeed this is apparent in many of the tobacco and AR studies discussed here (Field et al., 2007b; McHugh et al., 2010). These studies typically employ models of acute abstinence where smokers, for example, only observe a temporary period of abstinence prior to a testing session and are subsequently aware of being able to smoke after a session. The perceived availability of a drug is thought to play an important role in moderating cue-induced craving and attentional bias (Field & Cox, 2008), insofar that both processes are enhanced by the opportunity to use a substance. Unlike smokers who know that there is an opportunity to smoke after a laboratory session, those seeking treatment for smoking cessation in clinics are less inclined to think this is as possible after a treatment session. This study was an attempt at validating the findings from previous laboratory studies by using a more representative sample that were seeking treatment and trying to quit, but it failed to confirm the earlier findings. We should therefore be cautious in generalizing data derived from laboratory studies on attentional bias while the translational value is still unclear.

Since undertaking this trial, the study of attentional bias and AR in addictive behaviours has advanced to the use of mobile technology as both an assessment tool and delivery

system for training (Tiplady et al., 2009; Waters & Li, 2008). The use of portable electronic devices has several advantages over traditional methods. Firstly, it allows real-time data capture using EMA to study cognitive and motivational processes that may underlie relapse (Shiffman et al., 2008). Arguably, it is unclear whether attentional bias is more or less prominent under certain conditions, e.g. depending on the time of day, or in particular circumstances, e.g. the proximity of someone smoking. Laboratory and clinical settings do not typically mimic the natural environment in which people experience smoking-related cognitions and fluctuating motivational states. In a recent EMA study, heroin-dependent patients in treatment completed cognitive bias and affect assessments on a hand-held device at random times during the day and during self-reported temptations to use drugs (Waters et al., 2012). The authors found that selective processing biases were elevated during temptation episodes compared to other times during the day, and in the one hour preceding a temptation. Extending on these findings, Marhe et al. (2013) assessed whether processing biases and craving were predictive of relapse using similar EMA methods in heroin addicts; they found that patients who relapsed had greater Stroop bias and higher levels of craving during temptation episodes than those who did not relapse. Taking these findings together, it appears that cognitive associations in relapse may be more decipherable using EMA techniques than the methods traditionally used within laboratory settings. If these methods are able to identify the particular circumstances in which people are most susceptible to relapse, this could bring about a more targeted intervention approach to such instances.

Another advantage to the use of mobile technology in the study of attentional bias is that interventions like AR can be embedded within EMA. This approach not only enables

individuals to carry out training at any time of day, for example during temptation episodes when most at risk of smoking, but also obviates the time lag between training and assessments. At the time of writing, an EMA study (Kerst & Waters, 2013) examined the effects of daily AR on attentional bias in a sample of current smokers. The authors found that retraining delivered up to three times a day for seven days on a hand-held device reduced attentional bias towards smoking-related cues over time, in comparison to a control condition. However, this reduction in the AR group was only apparent after a few days. Attentional retraining also reduced cued craving following presentation of a picture with smoking and non-smoking features. Of particular note is that these retraining effects were not found in the laboratory session at the end of the study, which echoes the findings of this study. Again, this may be due to the time lag between training and laboratory assessments, implying that there are temporal effects of retraining. Alternatively, it may be that retraining effects are context-specific and more pronounced in the environment in which retraining occurs. As mentioned previously, further research using EMA methods and AR in a variety of contexts may shed light on any moderating effects of the environment. While it remains to be seen if there is any clinical benefit of daily retraining using EMA methods, these findings do show some promise in the use of AR procedures delivered in a smoker's natural environment.

In summary, we conducted the first clinical trial of attentional retraining in smokers attempting smoking cessation. We found that multiple sessions of AR - delivered weekly in NHS stop smoking clinics - had no effect on attentional bias, craving, withdrawal symptoms or relapse in smokers. Furthermore, attentional bias was not associated with any clinical outcomes. Overall, there are no clinical benefits of AR procedures in



treatment-seeking smokers and they should not be used as a therapeutic intervention in their current form.

## **CHAPTER 6: GENERAL CONCLUSIONS**

### **6.1 Summary of thesis**

The objective of the research outlined in this thesis was to develop, test and evaluate attentional retraining procedures in smokers. Underlying this objective was the aim of increasing our understanding on the phenomenon of attentional bias and its relation to other motivational processes and clinical outcomes in smoking cessation.

I began with a laboratory study to pilot the length of an AR procedure for clinical use (Chapter 2); this study informed the design of a protocol for a clinical trial of AR in smokers attempting to quit (Chapter 3). I reported on the outcomes of the trial, firstly on the feasibility of delivering AR in a clinical setting and its acceptability to participants (Chapter 4) and secondly, on the efficacy of AR on attentional bias, craving, withdrawal symptoms and abstinence (Chapter 5). The purpose of this chapter is to provide an overall synthesis of this research and recommendations for future investigations.

### **6.2 Summary of findings**

In the laboratory study described in Chapter 2, I examined the effect of varying the length of AR on attentional bias, subjective craving, mood and withdrawal in a sample of current smokers. The aim of this study was to gauge how much training was acceptable for participants to carry out in a single session, without ceding efficacy. I found that AR, delivered on a modified visual probe task with either a short, medium or long block of training did not significantly reduce attentional bias when compared to a control

condition. Similarly I did not observe reliable retraining effects on craving, mood or withdrawal measured after training and following cue-exposure. The likelihood of making an error during training became greater as the block length increased, suggesting that it became more difficult for participants to attend to the task as the length of training increased. Furthermore, the efficacy of training appeared to reduce as more errors were made. No effects were observed on an additional cognitive bias task measure.

Unexpectedly, the sample did not show an attentional bias at baseline, which may in part explain the lack of retraining effects observed. There was some indication that for those who had an attentional bias from the outset, post-training attentional bias was less in the trained group than the control group.

Based on the findings of the laboratory study alone, I was unable to unequivocally establish the optimal amount of training to deliver in the clinical trial of AR described in Chapter 3. I reasoned that even though retraining effects were not apparent at any length of training in the laboratory study, two blocks of training - with a break in between - were likely to be acceptable to patients and practical to deliver in a stop smoking clinic. Rather than increasing the number of training trials within each session, delivering multiple sessions was preferred as evidence from previous retraining studies that used more than one session had shown clinically relevant effects (Amir et al., 2009a; Schoenmakers et al., 2010).

Following on from the laboratory study, I conducted a double-blind randomised controlled trial of AR in smokers who attempted to quit using NHS stop smoking

services. Five sessions of attentional retraining or placebo training were delivered weekly in clinic using a modified visual probe task. I examined the feasibility and acceptability of the trial by looking at the processes involved in carrying out the study and how well the intervention was received by patients (Chapter 4). Delays with NHS regulatory approvals and difficulties with recruitment were the main practical barriers of delivering the study. I randomised 119 participants into the trial, which was less than the 200 participants anticipated. The first stage of patient recruitment via GP practice invitation letters was poor and so the strategy was revised. Methods used to improve recruitment included increasing the number of sites to include community venues as well as GP practices, targeting a new population group from a database of smokers and using online advertising; the combination of these approaches did improve the number of recruits but the target sample could not be reached within the timescale of the trial. Although these practical barriers prevailed, attendance at clinic sessions were high, as were the number of retraining sessions completed. Drop out was approximately equal across groups and was mainly due to a quit attempt abandonment. Taken together, the intervention was feasible to deliver within stop smoking clinics, despite problems with general recruitment, which were unrelated to the attentional retraining.

Most participants found the AR procedure easy to understand and carry out. However, some participants felt that the length of training was too long and that the task induced boredom; thus, irrespective of the efficacy of AR, it is important to take into account such factors as they may deter smokers from using these procedures as a treatment during smoking cessation.

I reported on the efficacy of the intervention in Chapter 5, but found little evidence that AR affected attentional bias, urge to smoke, withdrawal symptoms, abstinence rates and time to first lapse. Attentional bias scores were marginally and non-significantly lower in those who received AR than PT, but the effects were too small to be clinically meaningful. Similarly, urge to smoke was lower among abstainers who received AR than PT, but again, these effects were negligible and not significant. I failed to observe any retraining effects on withdrawal symptoms, where in fact, a marginal increase was found in those who received AR than PT. The fact that the intervention had no impact on quitting or time to first lapse, indicates that AR had no real impact on preventing relapse to smoking in this sample of treatment-seekers.

These findings echo those of the earlier laboratory study, where I found that AR had little effect on attentional bias, subjective outcomes and behavioural outcomes. Similarly across both studies, I found that AR on the modified visual probe task did not generalize to the Stroop task. This is consistent with findings from previous studies, where retraining on one cognitive bias task has not shown effects on another (Field et al., 2007b; Field et al., 2009b; Schoenmakers et al., 2007). I found some tentative evidence that generalization of AR occurred in relation to novel stimuli in the ARTS study, however these findings are exploratory in nature given that a decrease in attentional bias towards untrained stimuli was only found in non-abstainers and did not extend to trained stimuli.

Unlike some previous studies, the observational findings from the ARTS study indicated that attentional bias was not related to several indices of dependence or clinical outcomes,

meaning that participants with higher levels of attentional bias at baseline did not necessarily have higher levels of dependence, craving or withdrawal. Furthermore, attentional bias did not predict abstinence whether measured by the visual probe task or the Stroop task. Coupled with the finding that AR failed to produce any corresponding changes in attentional bias on craving – in neither the laboratory study nor the clinical trial - the research findings discussed here therefore do not support a causal role of attentional bias on craving.

Perhaps most crucial to this discussion is the finding that attentional bias was not evident in the sample of treatment-seekers recruited to the ARTS study. This was also found in the earlier laboratory study with smokers and has been reported elsewhere (McHugh et al., 2010). I reasoned that retraining effects might be stronger in those exhibiting an attentional bias from the outset; this was true of smokers in the laboratory study, but not of treatment-seekers in the clinical study.

In the sections that follow, I will provide some of my own reflections and recommendations for the study of attentional bias and attentional retraining, based on the collective findings of the research presented in this thesis.

### **6.3 Reflections**

It is important to first consider some of the possible reasons why attentional bias was not associated with any subjective or behavioural outcomes in either of my studies, in light of

the propositions outlined in Chapter 1. At the same time, it is necessary to understand why I found no effect of AR on these aforementioned outcomes.

### ***6.3.1 Attentional bias – is it causally related to addiction?***

Many of the theoretical models discussed in section 1.3.1 make predictions that drug-related cues capture the attention of drug users automatically and that processes like craving may be interrelated and subsequently influence drug use (Franken, 2003; Robinson & Berridge, 2001; Ryan, 2002). Although some evidence from correlational studies indicates that attentional bias is associated with craving, drug use and relapse (see section 1.5), these studies do not reveal anything about the causal role of attentional bias in addiction. Furthermore, the number of tobacco studies investigating this relationship, particularly in treatment-seeking or abstaining smokers is scarce.

Studies that experimentally manipulate attentional bias including the studies conducted here, provide the best evidence of causality. In the studies reviewed in section 1.4.2, most were able to manipulate attentional bias either towards or away from smoking or alcohol-related cues, but corresponding effects on subjective outcomes like craving were weak. Moreover, a relationship between attentional bias and craving has only been found in train-to-attend manipulations and mainly observed in certain groups, e.g. male participants only (Attwood et al., 2008) and those aware of the experimental contingencies (Field et al., 2007b). My studies, like all previous investigations involving train-to-avoid manipulations, found no evidence of a relationship between attentional bias and craving.

The evidence here and in other AR studies leads us to believe that attentional bias and craving are unrelated constructs; however one possible reason why I found no association could be because of difficulties in measuring both attentional bias and craving. I found no evidence of attentional bias in the study on smokers (Chapter 2) or treatment-seekers (Chapter 5) but we know that drug-users have exhibited attentional bias in many other studies (section 1.3.2). Indirect task measures - the visual probe task and the pictorial Stroop task - were used in both studies to assess attentional bias, although as I discussed in section 5.4.4, some investigators suggest that these measures may not be reliable (Ataya et al., 2012a). Similarly, there is much contention over the measurement of craving (Sayette et al., 2000; Tiffany & Wray, 2012). For example, self-report measures such as the QSU and MPSS rely on a smoker's ability to recognise and recall their experiences of craving. Nevertheless, if craving had been measured accurately even with a poor measurement of attentional bias, a retraining effect on craving would still be apparent had the intervention been successful. This view is reinforced by evidence from pharmacotherapy trials, where medication effects appear to be mediated through craving measured by similar measures (West et al., 2008). Altogether, the same argument holds for other variables where I found no associations and an absence of retraining effects on attentional bias, withdrawal symptoms, lapses and relapse outcomes.

Another point worth considering is that the studies conducted in this thesis focused on the measurement of maintained attentional bias rather than biases in the initial orienting of attention. As I discussed in section 1.3.2.2, these two subcomponents of attention may



have state-like or trait-like qualities. Similarly, as I discussed in section 1.4, craving may also be regarded as both state and trait phenomena. I speculated that maintained attentional bias may be a state-like construct and arises in situations of high cravings, while the initial orienting of attention may be a more persistent trait-like construct. Based on this premise, one might expect to see an association between maintained attentional bias and episodic cravings, particularly in treatment-seeking or abstinent smokers who are likely to experience high cravings when deprived of nicotine for example. In my clinical trial however, this may have been difficult to detect as participants were tested in a satiated state when maintained attentional bias was not evident. That said, participants in the earlier laboratory study were tested in a nicotine deprived state, yet the sample again did not exhibit maintained attentional bias at baseline and no associations with craving were found. Based on these studies alone, it is unclear whether certain states impact on attentional bias and associations with craving, given that there were several differences in smoking dependence and levels of nicotine deprivation across and within the studies that complicated this investigation. Understanding the extent to which both the initial orienting of attention and maintained attention resonates in smokers and the circumstances in which they might be found, may help clarify these issues.

Alternatively, an association between attentional bias, craving and my other clinical outcomes may not have been found for other reasons. It could be that the AR intervention was effective but the study lacked statistical power to detect an intervention effect. Indeed, I did not reach the desired number of participants required according to my sample size calculations. Another reason could be that the AR intervention was not effective in its current form but still has the potential to work if modifications to the

design are made (see section 6.3.2.1). Alternatively, it could be that AR simply did not function as a way of changing attentional bias and smoking behaviour, which altogether obviates an investigation of any causal relationship.

In light of the considerations above, I believe it is difficult to draw conclusions on whether attentional bias is causally related to addiction. Given that attentional bias was not related to any key variables associated with tobacco addiction in my studies indicates that it could be a by-product of addiction rather than a causal agent, as suggested by some investigators (Hogarth & Duka, 2006). However, before any definitive conclusions are drawn, it is important to ascertain whether the measures we are using are in fact reliably and accurately measuring attentional bias and other processes. Secondly, we need to establish whether modifications to the design of AR procedures are required in order for retraining effects to occur. Only then can we determine the true nature of a relationship between attentional bias and addiction.

#### *6.3.1.1 Recommendations: improving the precision of measurements*

Using better techniques to measure cognitive biases and refining existing procedures are ways of increasing the accuracy of attentional bias assessments. We might also uncover processes that would have otherwise gone undetected. Additionally, by making methodological improvements we increase the precision by which we measure attentional retraining effects on attentional bias. For example, direct measures, such as eye-tracking, are considered as more ecologically reliable indexes of attention than indirect measures (Field & Cox, 2008). Eye-tracking can be used to measure both the initial orienting of

attention and maintenance of attention, providing a method of investigating the extent to which different components of attentional bias can be considered as state-like or trait-like constructs. In conjunction with indirect measures, direct measures may be able to tap into these attentional processes more readily.

While direct measures may be more able to detect attentional bias if it is present, indirect measures are more practical and, as I have shown in Chapter 4, feasible to deliver in a clinic setting. The visual probe task and Stroop task are most often used for assessing and modifying attentional bias and so further work is warranted on refining and improving the reliability of these measures.

One way of increasing the reliability of the Stroop and visual probe task assessments could be to use more ecologically valid stimuli, i.e. pictures that participants are more accustomed to seeing in their everyday environment. As in Conklin et al. (2010), it may be worthwhile if participants took pictures of their real-world smoking and non-smoking environments to use as stimulus material in the visual probe task or Stroop task.

Another way of increasing the precision of measurements could be with the use of EMA methods. Administering the visual probe task or Stroop task on a hand-held device in a smoker's natural environment may be more capable of assessing attentional bias and naturally occurring processes like craving and withdrawal as they happen. It is plausible that smokers do not necessarily experience the same cognitions and motivations in a

laboratory or clinical setting as their natural environment. EMA could capture times in which smokers might be more prone to show attentional bias, or experience craving and withdrawal, for example in response to real-world smoking cues. Although, understanding what type of cues trigger these processes depends somewhat on a smoker's ability to report that they have attended to particular cues. There are numerous cues in the environment that a smoker will be less consciously aware of that could influence attentional bias, craving and withdrawal processes, but these would remain difficult to capture using EMA methods.

While different tasks appear to measure different aspects of attention depending on the time of assessment, it may be worthwhile to shorten the duration of stimulus presentations. Both studies conducted here used a stimulus onset asynchrony (SOA) of 500 ms, which is likely to reflect the maintenance of attention rather than the initial orienting of attention as discussed in section 1.3.2.2. The initial orienting of attention can only be captured at shorter stimulus durations, for example, of less than 200 ms [e.g. Field et al. (2009b) demonstrated that smokers exhibited attentional bias at an SOA of 50 ms], or by using direct measures such as eye tracking to measure the initial direction of eye movements (Field et al., 2004; Mogg et al., 2003). While the participants in my study did not show maintained attentional bias, it may be possible that attentional bias was present at the initial orientation stage. Speculatively, it could be that attentional bias at the earlier stages of attentional processing is more strongly associated with craving and relapse than later stages, although Field et al. (2009b) did not find an association between attentional bias and urge to smoke at an SOA of 50 ms.

Finally, it is important to consider the timing of attentional bias assessments in a treatment-seeking population. Although the sample in my clinical trial were recruited during a time in which they were thinking of stopping smoking, they were in fact tested in a satiated state when attentional bias may have been low. As discussed in section 1.3.2.2, biases in maintained attention –the principal measure in my clinical trial – may be regarded as a state-like construct which means that these slower attentional processes may only transpire in certain situations, e.g. when nicotine deprived. This may in part explain why I did not observe an attentional bias in the sample at baseline and the lack of association between attentional bias and my clinical outcome measures. Testing participants during the baseline period while they are still smoking and again on the first day of abstinence might address these questions.

### ***6.3.2 Attentional retraining procedures – are they effective in treatment-seeking smokers?***

On balance, a likely explanation of why I found no associations and no attentional retraining effects is that the intervention simply did not work. The intervention did not change cognitive bias processes or smoking behaviour overall. Considering all of the evidence discussed in section 1.4.2, it is clear that AR procedures designed to train attention away from smoking-related cues have not led to reductions in craving or led to reliable changes in other indices of smoking behaviour. Unlike the improvement in clinical symptoms found in clinically anxious patients or delayed relapse outcomes found in alcohol-dependent patients (section 1.7), I found no similar effects of AR in treatment-

seeking smokers. As the first study to test the efficacy of a tobacco-related AR procedure in a clinical population, I believe that there is no direct clinical benefit of AR procedures for smokers, as they currently stand.

Both studies followed the basic design of the AR procedures of previous tobacco-related retraining studies (Attwood et al., 2008; Field et al., 2009b; McHugh et al., 2010). As mentioned in the section above, the efficacy of AR could have been undermined by design issues. Although participants in the clinical study completed the majority of training sessions and the intervention was generally well received, some participants still were bored during the task probably due to its repetitive nature. As such, participants may not have been effectively trained if they were not attending to the task. Clearly, these laboratory-based procedures still require refinement and adaptation if they are intended for clinical use.

#### *6.3.2.1 Recommendations: modify the design of attentional retraining procedures*

It is worth noting that AR has been successful on reducing time to relapse in alcohol-dependent patients who were given positive feedback on performance and instructed to set goals to improve future performance (Schoenmakers et al., 2010). It is plausible that these additional interactive features of retraining work in two ways; positive feedback provides encouragement that the task is being performed well, while goal setting might increase engagement through motivation to meet certain targets. It could be speculated that both techniques could enhance the efficacy of retraining by increasing the likelihood of participants attending to a task. Individual learning curves could be inspected to

examine adherence over the course of a session to establish whether these techniques are worthwhile.

The number of training trials used in my studies may have been insufficient to produce a retraining effect; all other addiction-related retraining studies have employed more than double the 192 trials used in my clinical trial. I initially reasoned that multiple sessions might offset the need to increase the number of training trials within each session, although this assumption may have been wrong. Another way of delivering a higher ‘dose’ of training would be to increase the frequency of training and deliver sessions in a shorter period of time; indeed this method has been successful in producing the predicted changes in attentional bias in non-treatment seeking smokers (Kerst & Waters, 2013).

Finally, as discussed in section 6.3.1.1, if attentional bias was present during the initial orientation stage of attention, it would be important to design an AR procedure that could target this early stage of attentional processing. I adopted an SOA of 500 ms to measure and train participants in my studies but this SOA is unlikely to assess and change biases exhibited at the initial orientation stage. Considering that biases in the initial orienting of attention may be regarded as more of a consistent trait in drug users than maintained attentional bias, these processes may in fact be less amenable to change using AR procedures. Prior to developing an experimental manipulation to tackle these early attentional processes, it is necessary to establish if they are in fact important in the maintenance of addictive behaviours as they have not been studied as extensively as later processes.

## **6.4 Closing statements**

The aim of this thesis was to further our understanding of attentional bias and AR procedures in smokers. Firstly, a causal role of attentional bias in tobacco addiction is unsupported by the empirical studies reported in this thesis. Secondly, while AR procedures are feasible to deliver within NHS SSS, they are of no real benefit to smokers attempting to stop smoking.

In the context of previous studies, although some relate attentional bias to craving and relapse, the association between constructs is often weak and the findings are mixed. Overall, there is a lack of empirical research investigating this relationship, particularly in the case of smokers. On this basis, I believe that it is premature to conclude that attentional bias has no role in tobacco addiction. Instead, I agree with Ataya et al. (2012b) and believe that we are faced with the challenge of knowing that attentional bias exists in drug-users - be that in certain individuals or groups - but we may not necessarily have the right measures to consistently and reliably assess it. I would suggest that we turn our attention to improving the ways we measure cognitive processes, in order to better understand how they might relate to drug-taking behaviour.

As a clinical intervention, previous research in alcohol and anxiety indicates that the use of AR procedures lead to successful treatment effects in clinical populations. In marked contrast, my clinical trial revealed that AR does not reduce attentional bias, craving,



withdrawal symptoms or relapse in smokers seeking to quit. Altogether, there is not enough evidence on the efficacy of these procedures in the treatment of addictive behaviours, as only one other randomised controlled trial has investigated the effect of AR in alcohol abusers. It is clear that AR procedures for smokers should not be used in their current form and that both the assessment and any intervention to modify attentional bias needs improvement prior to any further investigation on their clinical value.

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## APPENDICES

### Appendix 1. Laboratory study participant information sheet

#### INFORMATION SHEET

##### Attentional Bias Retraining among Cigarette Smokers

You are being invited to take part in a research study because you are a cigarette smoker who smokes at least 5 cigarettes per day. Before you decide, it is important for you to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with friends, relatives or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

##### *What is this study about?*

This is a study to measure the effects of exposure to smoking-related pictures on subsequent cravings for cigarettes.

##### *Why have I been chosen?*

You are a cigarette smoker, aged 18 to 40. You should smoke at least 5 cigarettes per day, and should not be using other illicit drugs (except cannabis).

##### *Do I have to take part?*

Participation in the study is entirely voluntary. It is up to you to decide whether or not to do this. If you do decide to take part, we would ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep. If you decide to take part you are still free to withdraw from the study at any time. If you decide not to take part, or to withdraw, you do not have to give a reason, nobody would be upset.

##### *What would happen if I took part?*

You would first give a breath sample to confirm your smoking status, and then complete some short questionnaires. You would then be asked to complete a computer-based reaction time task, during which you would be presented with smoking-related and neutral pictures.

Next, you would be presented with a series of smoking cues, and be asked to rate your mood and craving for cigarettes.

You would then be given another computer-based reaction time task. After this you would have the opportunity to ask questions about the study, and the hypotheses that we are testing.

*What are my responsibilities?*

We would ask you to avoid smoking for 12 hours prior to the study. This would be confirmed by a breath sample when you arrive for testing, and if you were found to have smoked in the past 12 hours we would have to re-schedule your visit.

*What are the risks of taking part?*

You might experience moderate cravings for cigarettes during and immediately after the experiment, but we do not expect these effects to last very long.

*How would I benefit from participating?*

You would not benefit from taking part. However, you would be reimbursed for your participation (£10 total).

*How would we use the results of the research?*

These results may eventually be published in a scientific journal, and may also be reported at scientific meetings.

*Why is this study useful?*

Understanding the effects of smoking-related cues on cravings for cigarettes is important in helping to explain why people smoke. We are attempting to understand more about how the impact of smoking-related cues differs between people and across situations.

*Would I be able to know the results of the experiment?*

We won't be giving out individual results of the study, since all the data would be kept entirely confidential and anonymous. However, you would have the opportunity to ask questions about the study once you had taken part.

*Would my taking part in this study be kept confidential?*

All data collected in this study would remain confidential and would be available only to research staff directly involved in the study. It would not be possible to identify you by name from any aspect of reporting for this research study.

*Other information*

Your participation in the study is voluntary. Should you decide to take part, you would be asked to sign a consent form.

If you have any questions at any time about the study, please do not hesitate to contact the research team at the Department of Experimental Psychology at the address provided.

Main contacts:

Miss Rachna Begh

\_\_\_\_\_

\_\_\_\_\_

Dr Marcus Munafò

\_\_\_\_\_

\_\_\_\_\_

## Appendix 2. Laboratory study consent form

### CONSENT FORM

#### Attentional Bias Retraining among Cigarette Smokers

Researcher: Miss Rachna Begh

Participant ID:

Please Initial Boxes

- |    |  |                      |
|----|--|----------------------|
| 1. | I confirm that I understand the nature and purpose of the procedures communicated to me on a separate information sheet.   | <input type="text"/> |
| 2. | I understand that the experiment is designed to promote scientific knowledge, and that I have had the opportunity to ask questions.                                      | <input type="text"/> |
| 3. | I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.  | <input type="text"/> |
| 4. | I understand that a numerical code will replace my name so that my data can remain confidential and that I will not be identified in any way when research is published. | <input type="text"/> |
| 6. | I agree to the University of Bristol recording and processing the data I provide during the course of this study unless I state otherwise.                               | <input type="text"/> |
| 7. | I understand that all data will be collected and stored in accordance with the Data Protection Act (1998), and may be stored and processed electronically.               | <input type="text"/> |
| 8. | I understand that data will be used for the purposes set out in the information sheet, and my consent is conditional on compliance with the Data Protection Act (1998).  | <input type="text"/> |
| 7. | I agree to take part in the above study.   | <input type="text"/> |

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**Appendix 3. Laboratory study questionnaire**

**UNIVERSITY OF BRISTOL**

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Department of Experimental Psychology

8 Woodland Road

University of Bristol

Bristol

BS8 1TN

**CRF**  
**PARTICIPANT**  
**STUDY DAY**

**Study: Attentional bias retraining among cigarette smokers.**

**Ethics Number: 040310491C**

*Principal Investigator:*

Dr Marcus Munafò

*Investigators:*

Dr Angela Attwood

Miss Rachna Begh

*Please mark one answer for each question.*

1. How soon after you wake up do you smoke your first cigarette?

- ☐ Within 5 minutes
- ☐ 6-30 minutes
- ☐ 31-60 minutes
- ☐ After 60 minutes

2. How many cigarettes / day do you smoke?

- ☐ 10 or less
- ☐ 11-20
- ☐ 21-30
- ☐ 31 or more

3. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?

- ☐ Yes
- ☐ No

4. Do you smoke more frequently during the first hours after waking than during the rest of the day?

- ☐ Yes
- ☐ No

5. Do you smoke if you are so ill that you are in bed most of the day?

- ☐ Yes
- ☐ No

6. Which cigarette would you hate most to give up?

- ☐ The first one in the morning
- ☐ Any other

*A number of statements which people have used to describe themselves are given below.*

*Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers.*

*Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.*

NOT AT ALL	SOMEWHAT	MODERATELY	VERY MUCH SO
------------	----------	------------	--------------

- |  |                       |                       |                       |                       |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| 1. I feel calm                                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. I feel secure                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. I am tense  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. I feel strained                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 5. I feel at ease                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 6. I feel upset                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 7. I am presently worrying over possible misfortunes | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 8. I feel satisfied                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 9. I feel frightened                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 10. I feel comfortable                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 11. I feel self-confident                            | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 12. I feel nervous                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 13. I am jittery                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 14. I feel indecisive                                | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 15. I am relaxed                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 16. I feel content                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 17. I am worried                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 18. I feel confused                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 19. I feel steady                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 20. I feel pleasant                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |



*A number of statements which people have used to describe themselves are given below.*

*Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you generally feel. There are not right or wrong answers.*

*Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.*

ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
--------------	-----------	-------	---------------

- |  |                       |                       |                       |                       |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| 1. I feel pleasant                                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. I feel nervous and restless                           | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. I feel satisfied with myself                          | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. I wish I could be as happy as others seem to be       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 5. I feel like a failure                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 6. I feel rested   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 7. I am "calm, cool and collected"                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 8. I feel that difficulties are piling up                | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 9. I worry too much over things that don't really matter | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 10. I am happy   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 11. I have disturbing thoughts                           | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 12. I lack self-confidence                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 13. I feel secure  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 14. I make decisions easily                              | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 15. I feel inadequate                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 16. I am content   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 17. Unimportant thoughts bother me                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 18. I can't put disappointments out of my mind           | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 19. I am a steady person                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 20. I become tense as I think over recent concerns       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

*Indicate how much you agree or disagree with each of the following statements by placing a single checkmark along each line between **STRONGLY DISAGREE** and **STRONGLY AGREE**. The closer you place your checkmark to one end or the other indicates the strength of your agreement or disagreement.*

*We are interested in how you are thinking and feeling right now as you are filling out the questionnaire.*

1. I have a desire for a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

2. Nothing would be better than smoking a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

3. If it were possible, I probably would smoke now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

4. I could control things better right now if I could smoke.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

5. All I want right now is a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

6. I have an urge for a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

7. A cigarette would taste good right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

8. I would do almost anything for a cigarette now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

9. Smoking would make me less depressed.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

*Using a vertical line, please mark on each scale how you feel in your current mood  
(i.e., right now).*

Happy

Extremely Not at all

I—I

Drowsy

Extremely Not at all

I—I

Depressed

Extremely Not at all

I—I

Anxious

Extremely Not at all

I—I

Energetic

Extremely

Not at all

I ————— I

Irritable

Extremely

Not at all

I ————— I

Craving a Cigarette

Extremely

Not at all

I ————— I

**Please do not turn over until you are  
instructed to do so**

*A number of statements which people have used to describe themselves are given below.*

*Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers.*

*Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.*

NOT AT ALL	SOMEWHAT	MODERATELY	VERY MUCH SO
------------	----------	------------	--------------

- |  |                       |                       |                       |                       |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| 1. I feel calm                                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. I feel secure                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. I am tense  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. I feel strained                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 5. I feel at ease                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 6. I feel upset                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 7. I am presently worrying over possible misfortunes | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 8. I feel satisfied                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 9. I feel frightened                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 10. I feel comfortable                               | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 11. I feel self-confident                            | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 12. I feel nervous                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 13. I am jittery                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 14. I feel indecisive                                | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 15. I am relaxed                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 16. I feel content                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 17. I am worried                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 18. I feel confused                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 19. I feel steady                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 20. I feel pleasant                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

*Indicate how much you agree or disagree with each of the following statements by placing a single checkmark along each line between **STRONGLY DISAGREE** and **STRONGLY AGREE**. The closer you place your checkmark to one end or the other indicates the strength of your agreement or disagreement.*

*We are interested in how you are thinking and feeling right now as you are filling out the questionnaire.*

1. I have a desire for a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

2. Nothing would be better than smoking a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

3. If it were possible, I probably would smoke now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

4. I could control things better right now if I could smoke.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

5. All I want right now is a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

6. I have an urge for a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

7. A cigarette would taste good right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

8. I would do almost anything for a cigarette now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

9. Smoking would make me less depressed.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE



*Using a vertical line, please mark on each scale how you feel in your current mood  
(i.e., right now).*

Happy

Extremely Not at all

I—I

Drowsy

Extremely Not at all

I—I

Depressed

Extremely Not at all

I—I

Anxious

Extremely Not at all

I—I

Energetic

Extremely

Not at all

I ————— I

Irritable

Extremely

Not at all

I ————— I

Craving a Cigarette

Extremely

Not at all

I ————— I

**Please do not turn over until you are  
instructed to do so**

*A number of statements which people have used to describe themselves are given below.*

*Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers.*

*Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.*

NOT AT ALL	SOMEWHAT	MODERATELY	VERY MUCH SO
------------	----------	------------	--------------

- |   |                       |                       |                       |                       |
|---|-----------------------|-----------------------|-----------------------|-----------------------|
| 21. I feel calm                                       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 22. I feel secure                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 23. I am tense  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 24. I feel strained                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 25. I feel at ease                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 26. I feel upset                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 27. I am presently worrying over possible misfortunes | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 28. I feel satisfied                                  | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 29. I feel frightened                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 30. I feel comfortable                                | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 31. I feel self-confident                             | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 32. I feel nervous                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 33. I am jittery                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 34. I feel indecisive                                 | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 35. I am relaxed                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 36. I feel content                                    | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 37. I am worried                                      | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 38. I feel confused                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 39. I feel steady                                     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 40. I feel pleasant                                   | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

*Indicate how much you agree or disagree with each of the following statements by placing a single checkmark along each line between **STRONGLY DISAGREE** and **STRONGLY AGREE**. The closer you place your checkmark to one end or the other indicates the strength of your agreement or disagreement.*

*We are interested in how you are thinking and feeling right now as you are filling out the questionnaire.*

1. I have a desire for a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

2. Nothing would be better than smoking a cigarette right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

3. If it were possible, I probably would smoke now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

4. I could control things better right now if I could smoke.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

5. All I want right now is a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

6. I have an urge for a cigarette.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

7. A cigarette would taste good right now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

8. I would do almost anything for a cigarette now.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

9. Smoking would make me less depressed.

STRONGLY DISAGREE \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_: \_\_\_\_STRONGLY AGREE

*Using a vertical line, please mark on each scale how you feel in your current mood  
(i.e., right now).*

Happy

Extremely Not at all

I—I

Drowsy

Extremely Not at all

I—I

Depressed

Extremely Not at all

I—I

Anxious

Extremely Not at all

I—I

Energetic

Extremely

Not at all

I—————I

Irritable

Extremely

Not at all

I—————I

Craving a Cigarette

Extremely

Not at all

I—————I

**Thank you – you are nearly at the end  
of the experiment!**

**Appendix 4. Laboratory study debriefing sheet****DEBRIEFING SHEET****Attentional Bias Retraining among Cigarette Smokers**

Thank you for taking part in this experiment. The aims of the project are two-fold: to reassess whether the experimental manipulation of attentional bias influences subsequent cue reactivity to smoking cues in cigarette smokers and to explore whether the amount of attentional bias manipulation affects the degree of cue reactivity exhibited.

Attentional bias, where images and objects that have become associated over time with drug use tend to “capture” ones attention, are thought to be an important component of addiction which predict relapse to drug use. For example, people addicted to nicotine tend to notice smoking-related words and pictures more quickly than those who are not.

It is possible to experimentally manipulate the extent to which people either focus their attention on, or away from, such words and pictures. Our original study found that experimentally-induced attentional bias for smoking-related cues was associated with greater subsequent cue-induced craving compared to induced attentional bias for neutral cues. In this study, we are reassessing this relationship by comparing 2 groups, where:

- a) Participants have their attention trained towards neutral cues because the appearance of the probe during the reaction time task is more likely to occur in the location of a neutral picture. This is the training group.
- b) Participants don't have their attention trained towards any particular cues because the appearance of the probe during the reaction time task occurs in the location of the smoking-related and neutral pictures with equal frequency. This is the placebo training group.

We are also investigating whether manipulating the length of training has an effect on attentional bias and cue reactivity. In each group, a third of participants either receive a low dose, medium dose or high dose of training/placebo training. The allocation of participants to training/placebo training and one of the three groups is random, and we won't break the code which identifies which participants were in which condition until the study is complete.

This research will hopefully enable us to better understand the biological basis of addiction, and reassess the link between attentional bias and craving for cigarettes. We may also be able to better understand the impact of different amounts of attentional retraining on attentional bias and reactivity to smoking-related cues. We are also interested in measures of mood and personality, since these may help us to understand why no two smokers are the same. This research may eventually lead to novel treatments for nicotine dependence.



MacLeod, C. et al. (2002). Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *J Abnorm Psychol* 111: 107-123.

Attwood, A. S., O'Sullivan, H., Leonards, U., Mackintosh, B., & Munafò, M. R. (2008). Attentional bias training and cue reactivity in cigarette smokers. *Addiction*, 103, 1875-1882.

## Appendix 5. Pre-training and post-training attentional bias scores by group and block length allocation

### a) Pre-training and post-training attentional bias scores by allocation to short block length

	Attentional retraining (n=11)	Control (n=12)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	624.23 (93.03)	638.88 (81.22)	-14.65	-0.4	0.69	(-90.21, 60.91)
RT for neutral stimuli	638.50 (93.76)	629.54 (67.48)	8.96	0.27	0.80	(-61.41, 79.33)
Attentional bias	14.27 (68.46)	-9.33 (33.25)	23.61	1.07	0.30	(-22.42, 69.63)
Post-training						
RT for smoking stimuli	636.68 (161.45)	596.04 (109.40)	40.64	0.70	0.49	(-81.58, 162.86)
RT for neutral stimuli	644.68 (162.17)	600.38 (103.09)	44.31	0.77	0.45	(-76.63, 165.24)
Attentional bias	8.00 (37.29)	4.33 (33.23)	3.67	0.25	0.81	(-26.91, 34.25)
Change score attentional bias	-6.27 (84.48)	13.67 (55.60)	-19.94	-0.67	0.51	(-81.43, 41.55)

RT - reaction time (milliseconds)

### b) Pre-training and post-training attentional bias scores by allocation to medium block length

	Attentional retraining (n=13)	Control (n=10)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	697.15 (102.71)	719.15 (180.83)	-22.00	-0.37	0.72	(-145.83, 101.84)
RT for neutral stimuli	685.61 (100.62)	730.05 (181.20)	-44.43	-0.75	0.46	(-167.70, 78.83)
Attentional bias	-11.54 (30.43)	10.90 (31.47)	-22.44	-1.73	0.09	(-49.45, 4.58)
Post-training						
RT for smoking stimuli	617.23 (112.01)	638.75 (113.22)	-21.52	-0.46	0.65	(-119.96, 76.92)
RT for neutral stimuli	616.12 (109.06)	664.70 (151.75)	-48.58	-0.90	0.38	(-161.51, 64.34)
Attentional bias	-1.12 (27.06)	25.95 (53.33)	-27.07	-1.59	0.13	(-62.46, 8.33)
Change score attentional bias	10.42 (51.34)	15.05 (61.25)	-4.63	-0.20	0.85	(-53.44, 44.18)

RT - reaction time (milliseconds)

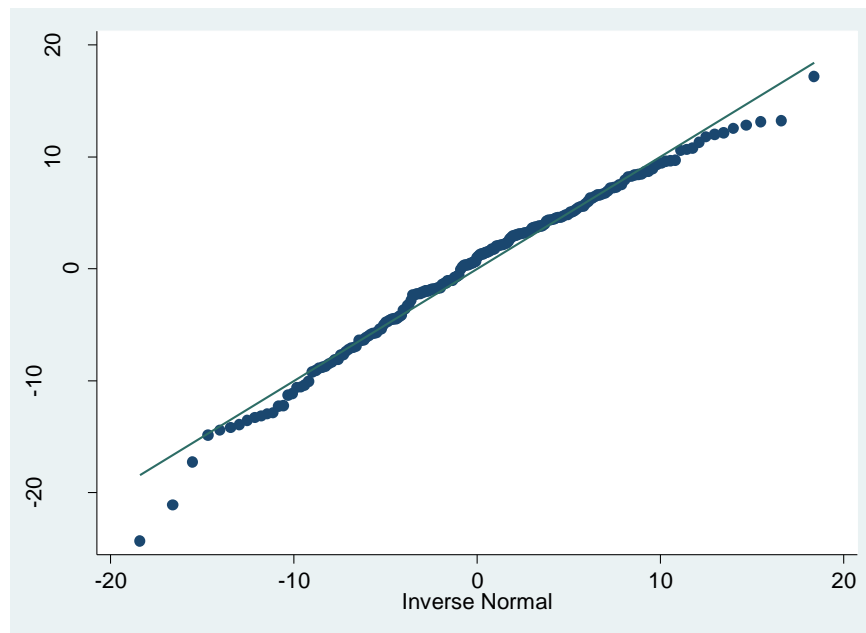
*c) Pre-training and post-training attentional bias scores by allocation to long block length*

	Attentional retraining (n=8)	Control (n=13)	Mean difference	t	p	95% CI
	M (SD)	M (SD)				
Pre-training						
RT for smoking stimuli	650.81 (183.53)	678.58 (114.43)	-27.76	-0.43	0.67	(- 163.02, 107.49)
RT for neutral stimuli	665.00 (205.23)	682.42 (118.42)	-17.42	-0.25	0.81	(-164.26, 129.41)
Attentional bias	14.19 (51.75)	3.85 (47.13)	10.34	0.47	0.64	(-35.63, 56.32)
Post-training						
RT for smoking stimuli	567.81 (101.09)	584.42 (88.81)	-16.61	-0.40	0.70	(-104.57, 71.35)
RT for neutral stimuli	590.75 (125.04)	580.08 (92.18)	10.67	0.23	0.82	(-88.54, 109.88)
Attentional bias	22.94 (31.16)	-4.35 (48.00)	27.28	1.43	0.17	(-12.76, 67.33)
Change score attentional bias	8.75 (56.28)	-8.19 (44.19)	16.94	0.77	0.45	(-29.14, 63.02)

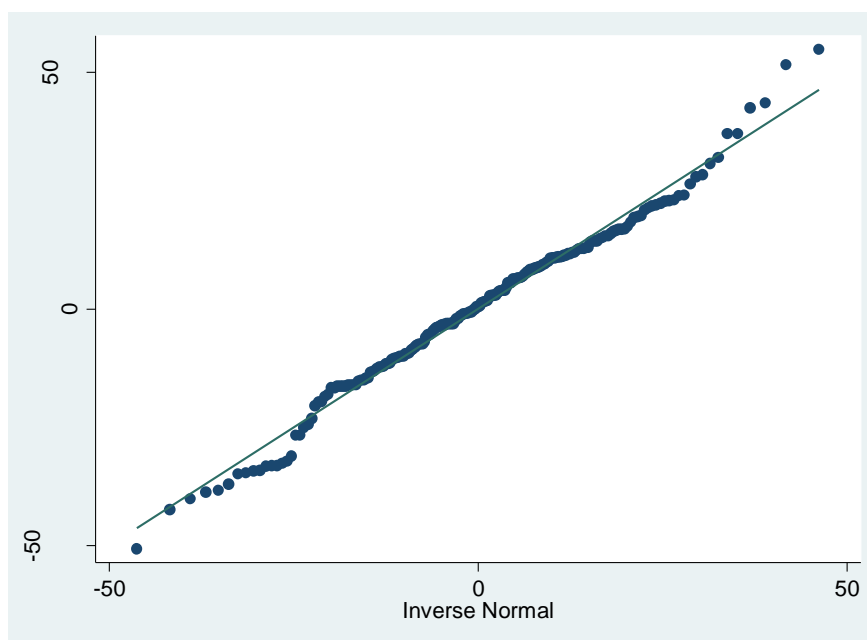
*RT - reaction time (milliseconds)*

**Appendix 6. Normal probability plots for QSU-Brief and VAS multi-level models**

*a) Example plot of residuals for fully specified model of QSU-Brief scores*

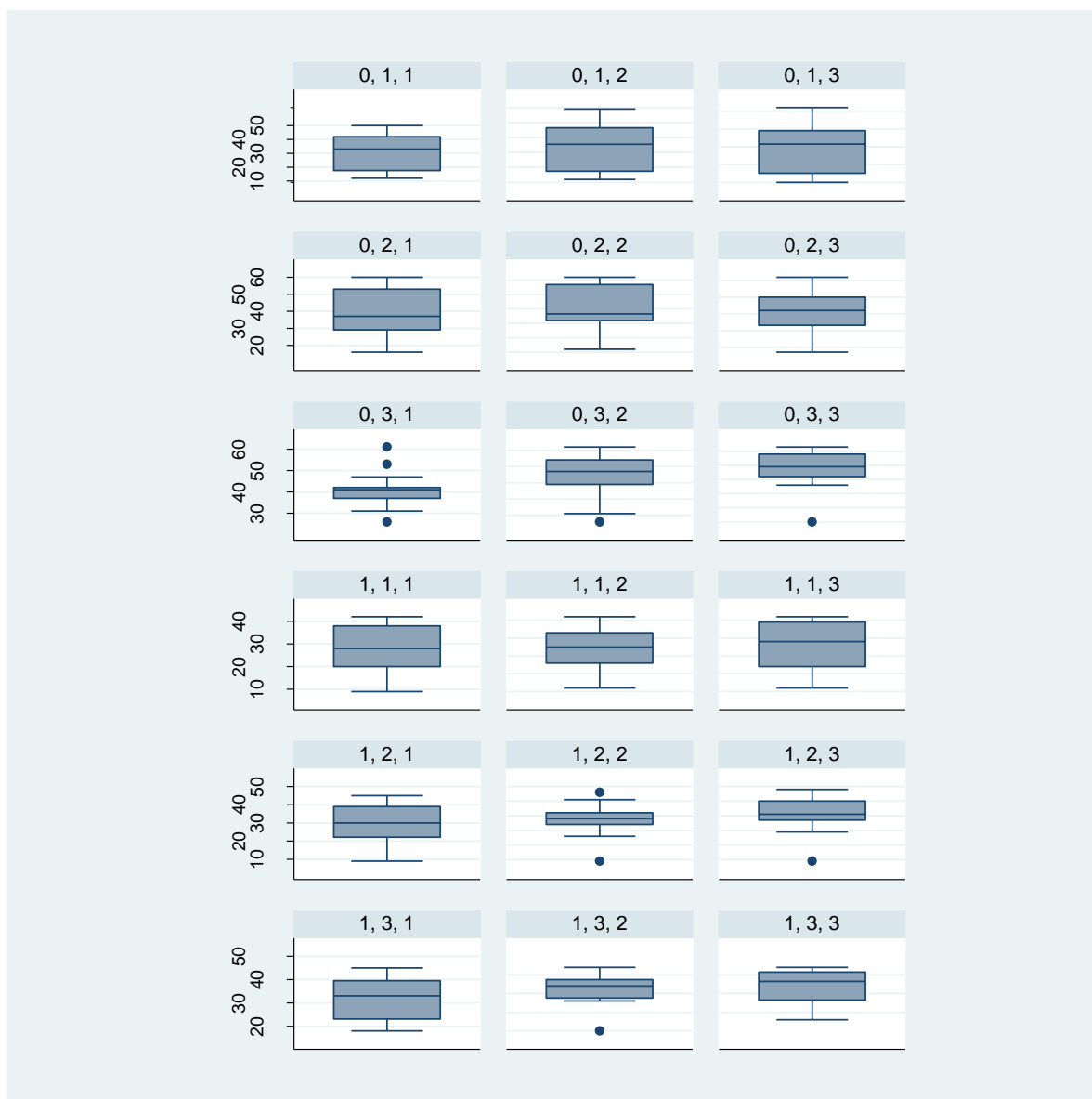


*b) Example plot of residuals for fully specified model of VAS scores*



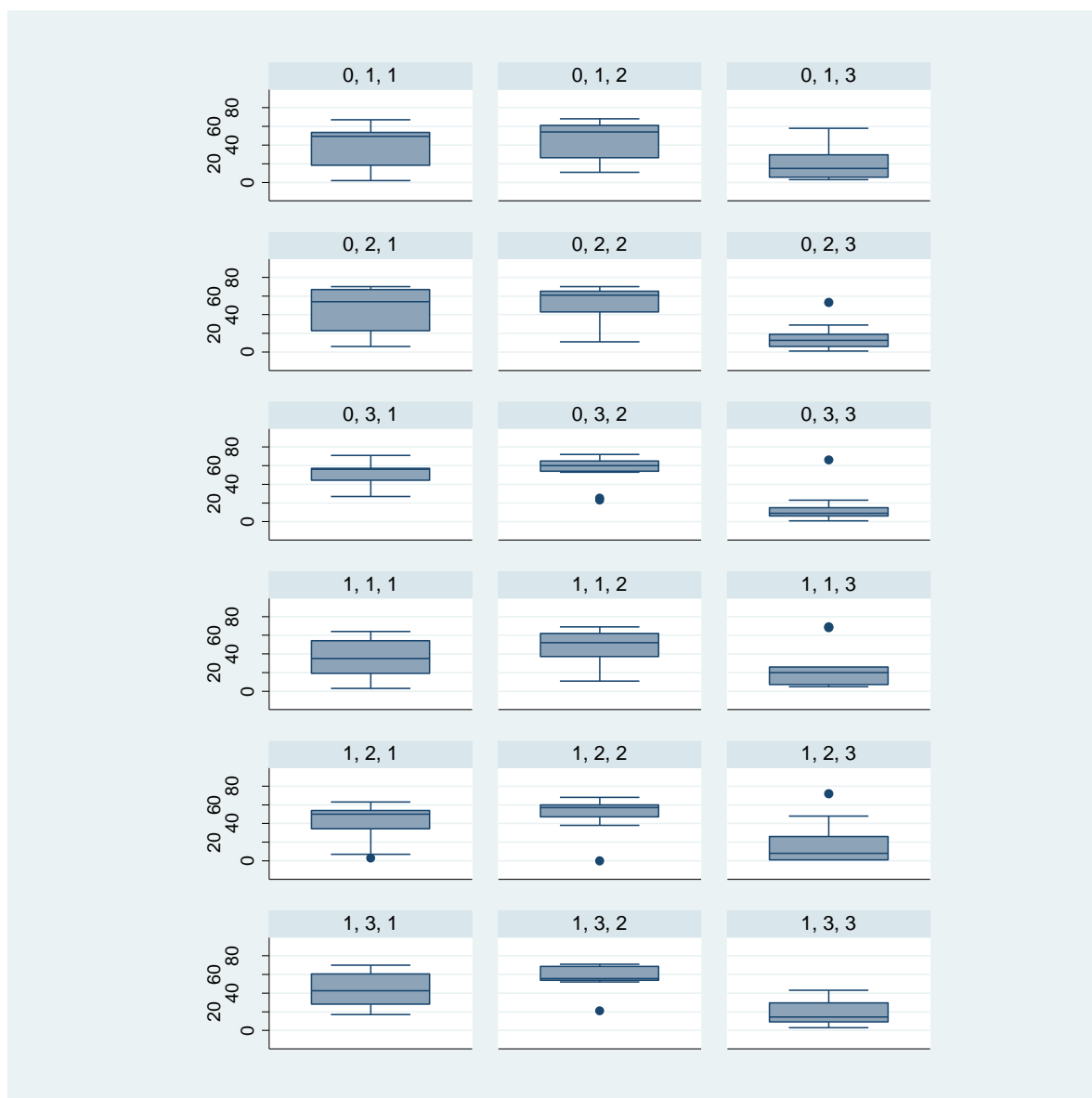
## Appendix 7. Box plots illustrating the distribution of QSU-Brief scores and VAS craving scores by group, block length and time

### a) Box plot of QSU-Brief scores



Plot headings follow the format [group, block length, time] where control=0, attentional retraining=1; short block length=1, medium block length=2, long block length=3; baseline=1, pre-exposure=2, post-exposure=3

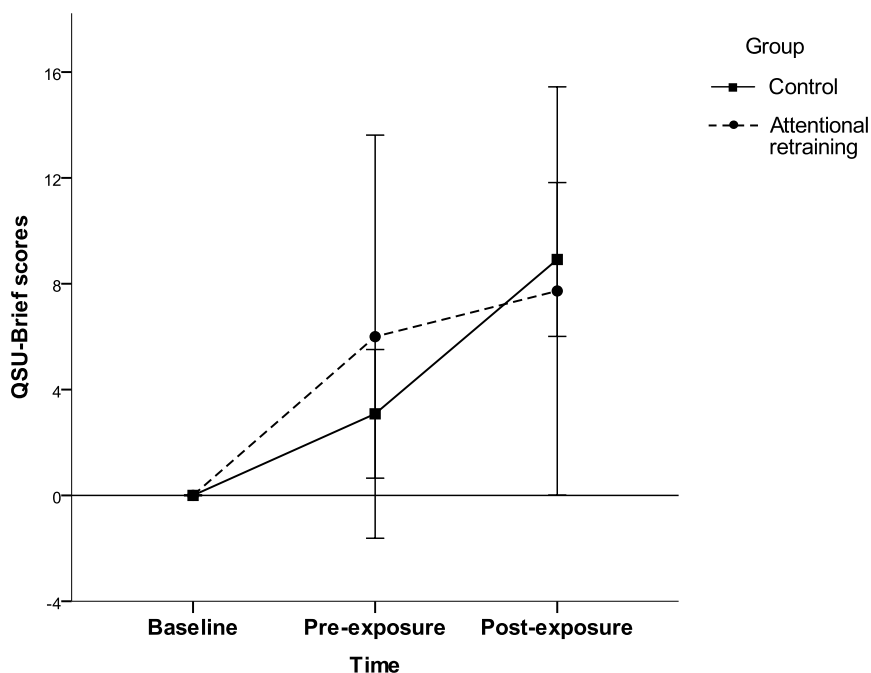
*b) Box plot of VAS craving scores*



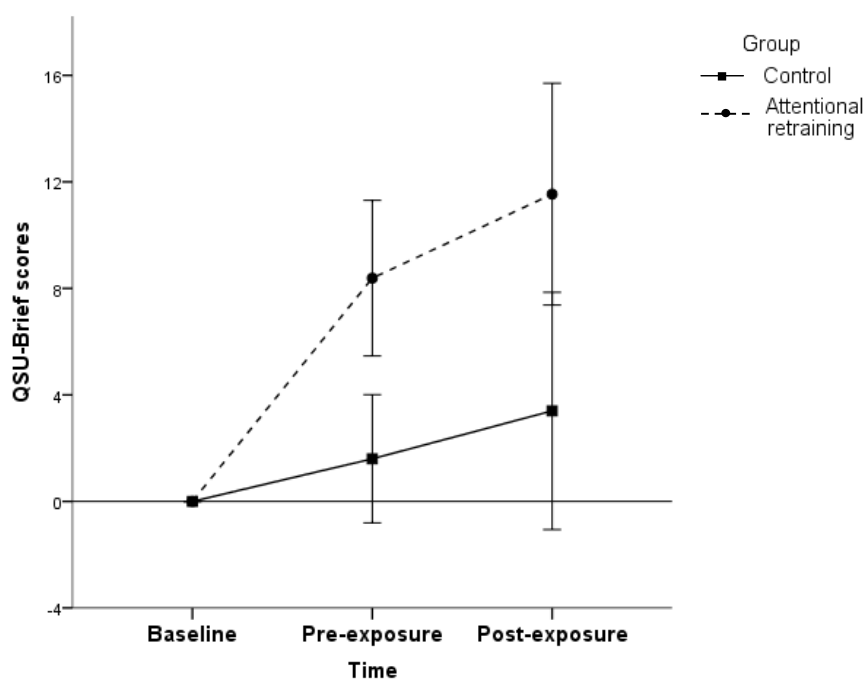
Plot headings follow the format [group, block length, time] where control=0, attentional retraining=1; short block length=1, medium block length=2, long block length=3; baseline=1, pre-exposure=2, post-exposure=3

**Appendix 8. Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group by block length**

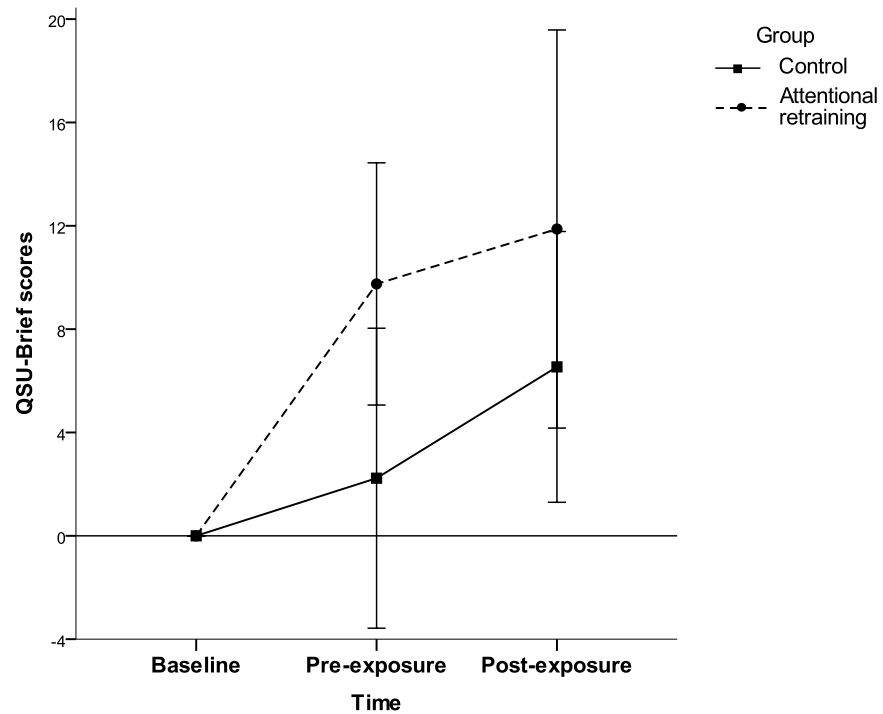
- a) *Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the short block length*



- b) *Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the medium block length*



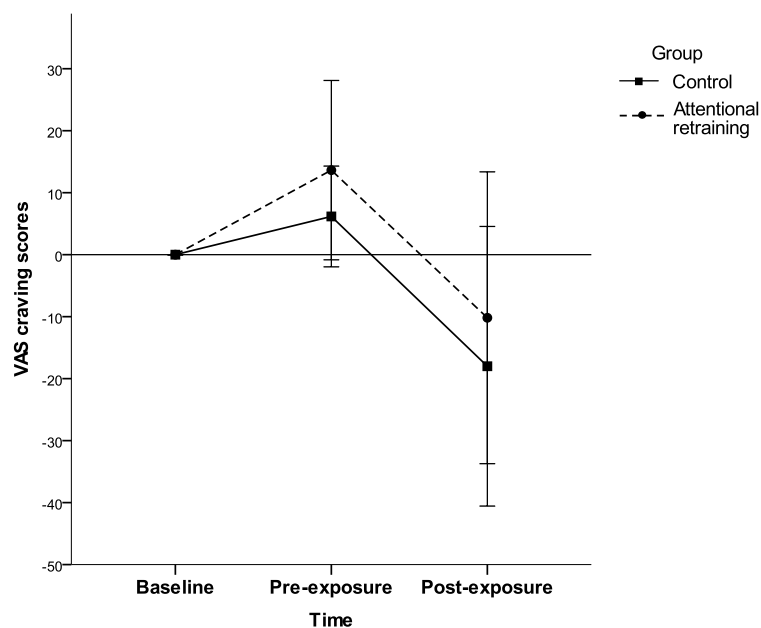
c) Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the long block length



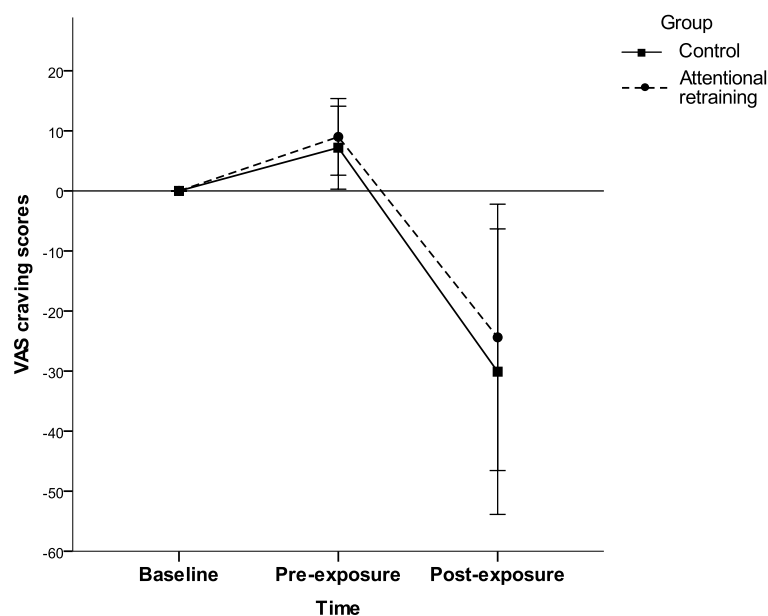


**Appendix 9. Mean (95% CI) change in VAS craving scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group by block length**

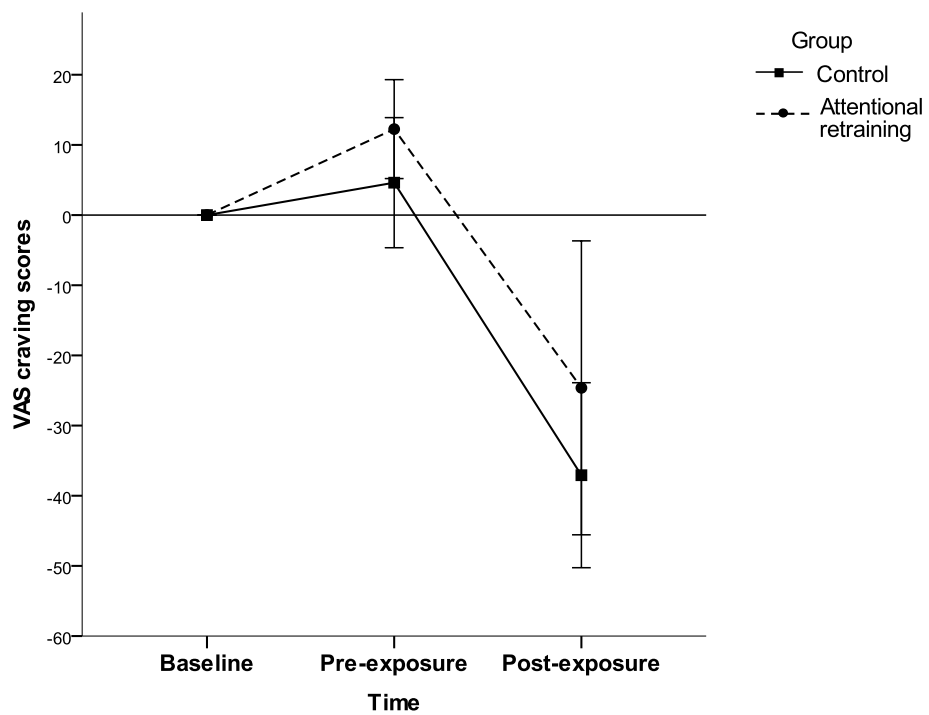
- a) *Mean (95% CI) change in VAS craving scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the short block length*



- b) *Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the medium block length*



c) Mean (95% CI) change in QSU-brief scores from baseline to pre-exposure and post-exposure in the attentional retraining group and control group at the long block length



## Appendix 10. Published ARTS trial protocol

Begh et al. *BMC Public Health* 2013, **13**:1176  
http://www.biomedcentral.com/1471-2458/13/1176



### STUDY PROTOCOL

### Open Access

# Attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS): Study protocol for a double blind randomised controlled trial

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## Abstract

**Background:** Smokers attend preferentially to cigarettes and other smoking-related cues in the environment, in what is known as an attentional bias. There is evidence that attentional bias may contribute to craving and failure to stop smoking. Attentional retraining procedures have been used in laboratory studies to train smokers to reduce attentional bias, although these procedures have not been applied in smoking cessation programmes. This trial will examine the efficacy of multiple sessions of attentional retraining on attentional bias, craving, and abstinence in smokers attempting cessation.

**Methods/Design:** This is a double-blind randomised controlled trial. Adult smokers attending a 7-session weekly stop smoking clinic will be randomised to either a modified visual probe task with attentional retraining or placebo training. Training will start 1 week prior to quit day and be given weekly for 5 sessions. Both groups will receive 21 mg transdermal nicotine patches for 8–12 weeks and withdrawal-orientated behavioural support for 7 sessions. Primary outcome measures are the change in attentional bias reaction time and urge to smoke on the Mood and Physical Symptoms Scale at 4 weeks post-quit. Secondary outcome measures include differences in withdrawal, time to first lapse and prolonged abstinence at 4 weeks post-quit, which will be biochemically validated at each clinic visit. Follow-up will take place at 8 weeks, 3 months and 6 months post-quit.

**Discussion:** This is the first randomised controlled trial of attentional retraining in smokers attempting cessation. This trial could provide proof of principle for a treatment aimed at a fundamental cause of addiction.

**Trial registration:** Current Controlled Trials ISRCTN54375405.

## Background

Although many people who smoke achieve short-term success with current smoking cessation interventions, the rate of relapse to smoking remains high. Over 75% of initially successful quitters return to smoking within a year, with relapse occurring most commonly in the first 6 months after cessation [1]. At present, there is insufficient evidence to support the use of

behavioural methods to prevent relapse in individuals achieving initial abstinence [2]. Most interventions have typically focused on Marlatt and Gordon's [3] 'skills' based approach, which attempts to teach patients to identify situations conducive to relapse and teach cognitive and behavioural coping skills to deal with these situations. However, there is no evidence that the skills based approach diminishes or delays relapse to smoking [4] and so new interventions are required.

More recently, there has been increasing interest in the influence of implicit cognitive processing biases on our understanding of the relapse process [5]. Attentional bias, where drug users show excessive attention towards drug-related cues in the environment, is well-documented

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in tobacco smokers and users of other drug substances [6,7]. Several theoretical models of attentional bias propose that through repeated drug use, drug-related cues appear appealing to drug users, 'grab' attention and become 'wanted' to the extent that behaviour is guided towards drug use relatively automatically [8,9]. Further theoretical models propose that increases in attentional bias are both a cause and consequence of high levels of craving [10]. Thus, smokers with high levels of craving may be more likely to search the environment for smoking-related cues, while prolonged attentional processing of smoking-related cues could increase urges to smoke. There is evidence that attentional bias is related to drug craving [11], although this relationship has been reported as somewhat weak [12]. Attentional bias has also been linked to an increase in the likelihood of relapse in smokers [13], alcohol users [14] and heroin addicts [15]. There is also strong anecdotal evidence that environmental and situational cues act as triggers for relapse in abstinent smokers. Control of attentional processes may therefore play a key role in preventing relapse among smokers who are attempting to quit, although current smoking cessation programmes delivered by the National Health Service (NHS) Stop Smoking Services (SSS) in the United Kingdom (UK) do not target attentional biases directly.

Several paradigms measure cognitive processing biases. The most common among these are the visual probe task [16] and Stroop task [17]. In the standard version of the visual probe task, pairs of pictures or words – one drug-related and one neutral stimulus – are presented briefly on a computer screen before a probe appears in the location formerly occupied by one of the pictures or words. Smokers, in comparison to non-smokers, have shown an attentional bias towards smoking by responding faster to probes that appear in the location of smoking-related stimuli rather than neutral stimuli [18,19]. Other drug users have shown an attentional bias towards drug-related stimuli of their choice; for example, cannabis users are faster to respond to cannabis-related stimuli than neutral stimuli [20]. Similarly, the addiction Stroop task has been used extensively to measure selective processing of drug-related stimuli [21]. Processing biases on the Stroop task have been demonstrated in smokers who are typically slower to colour-name smoking-related stimuli than neutral stimuli [22,23].

There is some evidence to suggest that cognitive processing biases are apparent in smokers even after attempts to stop smoking. The first study to explore this found that ex-smokers, who were enrolled in a smoking cessation programme and had been abstinent from smoking for at least 1 week, had an intermediate bias for smoking-related stimuli, in-between that of smokers and non-smokers [19]. In another study, smokers who were attempting to quit and smokers without such plans had similar levels

of attentional bias [24]. In contrast to these studies, two studies found that ex-smokers showed a similar level of processing bias as never-smokers, while smokers exhibited more bias than both other groups [23,25]. In both of these studies, ex-smokers had been abstinent for at least 6 months rather than recently abstinent from smoking. Thus, data are conflicting but it is possible that attentional bias persists early in a quit attempt and resolves with increased duration of abstinence although no study has examined this. However, if attentional bias persists for many months, we might speculate that if there are enduring effects of smoking cues after cessation as suggested in previous research, abstinence could be undermined in initially successful quitters.

Cognitive bias modification (CBM) procedures have been developed in an attempt to change cognitive processing biases using modified versions of the visual probe task and Stroop task [26-33]. CBM procedures are designed to augment or attenuate cognitive processing biases, providing not only a method of studying the causal relationship between attentional bias, craving and relapse, but also a potential treatment for attentional bias in clinical populations. Attentional retraining (AR) is most commonly used in the study of addiction-related attentional bias. Individuals with specific drug use patterns can be trained to increase or decrease attentional bias towards their drug of choice in train-to-attend and train-to-avoid manipulations, respectively [26,28-30,32]. In the train-to-attend manipulation, probes replace drug-related stimuli more frequently than neutral stimuli; by comparison in the train-to-avoid manipulation, probes replace neutral stimuli on a greater number of occasions. Consequently attention is trained towards one particular stimulus type.

Most investigations of AR in addiction have been conducted in laboratory studies of non-treatment seeking alcohol users [28,29,32] and more recently, tobacco smokers [26,30,31]. These studies have typically measured the effects of AR on subjective outcomes, e.g. craving and behavioural outcomes such as drug consumption as well as the change in attentional bias. In the first of these studies comparing a train-to-attend with a train-to-avoid manipulation, training towards alcohol-related stimuli was associated with increases in attentional bias, urge to drink and actual beer consumption. Conversely, training away from alcohol-related stimuli was associated with reductions in attentional bias and beer consumption but not urge to drink. The study was replicated with the inclusion of a control group that received no training towards any particular stimulus type; the predicted direction of change in attentional bias was observed in the groups trained to attend or avoid alcohol-related stimuli, as well as no change in attentional bias in the control group [29]. Alcohol craving increased among participants in the attend group, but



only for those who were aware of the experimental contingencies, i.e. participants who reported the relationship between the location of the probe and stimulus-presentation correctly in a post-task questionnaire. However, in contrast to the findings of the earlier study, there were no differences between groups in the volume of beer consumed. Schoenmakers and colleagues carried out a similar study where heavy social drinkers had learned to avoid alcohol-related stimuli and developed an attentional bias towards soft drinks, although training had no effect on craving or drink choice [32].

Only three laboratory studies have published findings on AR procedures in current tobacco smokers [26,30,31]. The first of these studies found that AR increased attentional bias in participants who were trained towards smoking-related stimuli and decreased attentional bias in those trained towards neutral stimuli [26]. Furthermore, when participants were measured on their response to a lit cigarette following the training procedure, greater increases in subjective craving were found in male participants who attended to smoking-related stimuli than those trained towards neutral stimuli. However, no effect of training on smoking topography (e.g. number of puffs taken, puff duration, etc.) was observed. In a replication of the study with a no-training control group, attentional bias was greater after training in the attend group than the avoid and no-training control groups, but these effects disappeared after 1 day [30]. Neither the train-to-attend or train-to-avoid manipulations had any effect on urge to smoke, although unlike in the previous study, no cue exposure task was used. No group effects of retraining on motivation to smoke were observed. McHugh and colleagues compared an avoid group with a no-training control group and found no change in attentional bias and no effects of retraining on subjective craving [31]. Unlike the two previous studies, no behavioural measures of tobacco-seeking were taken.

Collectively, laboratory studies of AR suggest that attentional bias can be modified and that, in some cases, corresponding changes in craving occur. While AR has not shown any effects on drug-taking behaviour in smokers, it is worth noting that laboratory studies of AR typically recruit samples of continuing smokers who are temporarily abstinent for the purpose of the experimental investigation. These smokers presumably have no motivation or intention to reduce their substance use in comparison to treatment-seeking smokers. Studies of AR in clinical populations are capable of addressing how attentional bias relates to real-world behaviour – particularly relapse – in addition to assessing the efficacy of AR as a clinical intervention.

Only two studies to date have examined the effects of AR in substance users seeking to reduce or abstain from drug use [27,33]. In an uncontrolled trial of AR,

hazardous and harmful drinkers interested in reducing their alcohol intake completed 2 or 4 weekly sessions of AR on a modified Stroop task, respectively [27]. After treatment was complete, processing biases towards alcohol-related stimuli reduced in both groups, as did alcohol consumption by approximately 10 Units/week (1 Unit is equivalent to 8 g of ethanol) for the harmful drinkers. These reductions were also maintained at the 3 month follow up. Uncontrolled trials in people seeking to change their behaviour are difficult to interpret, however. In the only randomised controlled trial of AR in substance users, Schoenmakers and colleagues found that alcohol-dependent patients were more able to disengage attention from alcohol-related stimuli than control patients after 5 sessions of AR on a modified visual probe task, given in addition to standard treatment [33]. Moreover, relapse was delayed by over a month in patients that received AR. While there appear to be promising effects of AR as a clinical intervention in alcohol abusers, little is known about the clinical value of AR procedures in smokers attempting to quit.

#### Rationale for the trial

Resumption of smoking by initially successful quitters is arguably the greatest public health challenge in smoking cessation. While there are few interventions at present that are known to reduce the risk of relapse to smoking [2], the development of new approaches like AR could be worthwhile. Despite evidence from laboratory studies indicating that attentional bias can be modified in tobacco smokers using AR procedures [26,30] and the success of such tasks on improving clinical outcomes in other addictions [33] and psychopathologies [34], no study has yet explored the clinical application of these procedures in treatment-seeking smokers.

We therefore propose a double-blind randomised controlled trial of multiple sessions of attentional bias retraining in smokers attempting smoking cessation (ARTS). This translational study offers the ability to both examine the benefits of AR on users of stop smoking services and provide findings to aid our understanding on the phenomenon of attentional bias and its relation to craving, withdrawal symptoms, lapses and relapse in smokers attempting to quit.

#### Aims and study questions

The aim of the study is to investigate the efficacy of an AR intervention on attentional bias and smoking cessation outcomes in smokers undertaking behavioural treatment. The following study questions will be addressed:

- 1) Can AR diminish attentional bias in smokers during cessation; are the effects evident across different cognitive bias tasks and different types of stimuli?

We will investigate whether AR – using multiple sessions – can lead to reductions in attentional bias in smokers who are attempting cessation. If retraining is successful, participants should be able to demonstrate that they can divert their attention away from smoking cues on a visual probe task. We expect AR to reduce the degree to which smokers notice smoking cues in their environment because they are trained away from attending to them. Similarly, if AR shows material reductions on one cognitive bias task, it is plausible that a reduction may be seen on another task measure – such as the pictorial Stroop task – if similar attentional processes are involved. Finally, if AR produces a global change in attentional bias and not just a task-specific change in bias towards smoking cues, then smokers should be able to transfer their ability to divert their attention away from other smoking cues that are not featured in the retraining procedure.

- 2) Does AR affect urges to smoke, cue-induced craving or withdrawal symptoms in smokers during cessation?

We will investigate the effects of AR on urges to smoke, cue-induced craving and withdrawal symptoms in smokers during their cessation attempt. If AR procedures are capable of reducing exposure by diverting attention away from smoking cues, this in turn could reduce the capacity of these cues to invoke craving and symptoms of withdrawal.

- 3) Do the effects of AR on attentional bias persist up to 6 months after cessation?

One marker for the success of AR procedures is to evaluate whether they produce enduring effects; this is particularly pertinent if the presence of attentional bias undermines abstinence [35]. As the durability of AR remains unclear at present, we will investigate whether the effects of AR are evident in smokers after their cessation attempt at follow-up assessments.

- 4) Does AR reduce the likelihood of relapse in smokers attempting cessation?

We will assess whether retraining can reduce the likelihood of relapse in smokers attempting to quit. If the ability to divert attention away from smoking-related cues during retraining translated to a smoker's natural environment, s/he might experience less exposure to the environmental cues that would normally trigger smoking; in time, this could weaken the stimulus–response association between smoking cues and smoking behaviour, thus reducing the likelihood of a lapse occurring. Alternatively, if attentional avoidance leads to less instances of craving, this may also in turn reduce the likelihood of relapse, given that craving predicts relapse [13,36,37].

### Methods/design

This is a double blind randomised controlled trial. Participants attending a 7-session weekly NHS stop smoking clinic will be individually randomised to either an intervention group consisting of a modified visual probe task with AR or a control group with placebo training (PT). Five sessions of AR or PT will be delivered. Both groups will receive nicotine replacement therapy (NRT) in the form of transdermal nicotine patches and standard withdrawal orientated behavioural support [38].

### Inclusion criteria

Participants will be required to meet the following inclusion criteria to be eligible for enrolment into the trial:

1. Aged 18 years or over.
2. Currently smoke at least 10 cigarettes per day or 12.5 grams of tobacco or have a value of at least 10 parts per million (ppm) for exhaled carbon monoxide (CO).
3. Have normal or corrected-to-normal vision.
4. Informed consent.
5. Are able and willing to complete all study procedures.

### Exclusion criteria

Participants will be excluded if they present with any of the following:

1. A medical condition that prevents them from seeing the computerised images properly, attending to the task, or pressing the keyboard buttons on the computer accurately, or completing any other study procedures.
2. Are currently using nicotine replacement therapy (NRT), bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture) that they are not willing to cease using and instead use study medication.
3. Have previously had severe skin reactions to nicotine patches or severe eczema or other skin diseases that make patch use hazardous or undesirable.
4. Have a severe acute or chronic medical or psychiatric condition or previously diagnosed clinically important renal or hepatic disease, which could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

### Withdrawal criteria

It is standard practice in smoking cessation trials to treat those who fail to attend appointments as having relapsed

[39]. Therefore, failure to attend will not be defined as withdrawal from the trial; we consider that the only withdrawals will be those in which the participant has asked to be withdrawn. We expect this in less than 5% of participants. This is standard procedure in smoking cessation studies.

#### Participant recruitment

Figure 1 shows the flow of participants through the trial. Participants will be recruited from West Midlands NHS SSS. A letter of invitation and a patient information sheet about the study will be sent from GP practices to patients that are registered on their databases as smokers. The letters will ask those patients who wish to take part in the trial to respond to the study team. In our experience, we anticipate that 5–10% will respond. Staff within the NHS SSS will also write to smokers with a history of failed quit attempts who are on their databases. Preliminary eligibility to participate will be assessed during telephone screening and potential participants will be booked in for an assessment session at the clinic site, similar to that arranged by the NHS SSS. Written informed consent will be obtained from all participants at the first session, which takes place 2 weeks prior to quit day.

#### Staff training

Research nurses and stop smoking advisors (SSAs) will be trained to deliver the intervention. All staff will complete a 2-day NHS stop smoking advisor course. They will also

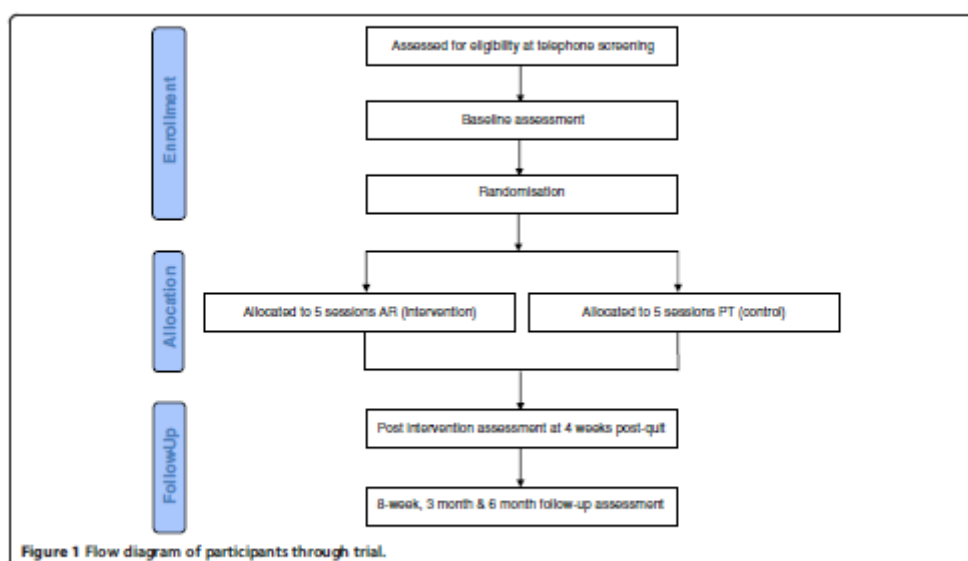
attend a training day in which they will be briefed on the clinical procedure on how to deliver each task and on use of the trial database. Prior to running a clinic, each member of staff will observe a baseline session and week -1 (randomisation) session delivered by the chief investigator. In turn, the chief investigator will observe the first two sessions delivered by each nurse/SSA involved in the study. Regular site visits will be conducted to check that the intervention is being delivered as per protocol.

#### Trial procedures

Participants in both trial arms will be seen weekly in clinics from 2 weeks prior to quit day up to 4 weeks post quit day. There are ten clinic sessions in total. Randomisation takes place at the second clinic session, which initiates the first of the 5 weekly AR/PT sessions. Follow up visits take place at 8 weeks and 3 months post quit day, with a final visit arranged at 6 months. Participants will be paid £15 to complete assessments at 3 month and 6 month follow-up sessions, as these are not therapeutic encounters. Participants will be reminded to attend their appointments by telephone or text message. Staff will complete a case report form (CRF) at each clinic visit, which contains a checklist of the trial procedures.

#### Randomisation

Participants will be randomised 1:1 to either AR or PT using a computer generated simple randomisation scheme, ordered in random permuted blocks of four. The sequence





was generated by the trial statistician and entered on to a dedicated online trial database by an independent programmer in the Primary Care Clinical Research and Trials Unit (PCCRTU) at the University of Birmingham. At 1 week prior to quit day, at the start of the clinic session, the therapist will access the randomisation section of the trial database and click on a button that reveals a letter ('A' or 'B') to reveal the training task to which the participant is allocated. The training tasks are contained within two folders labelled 'Training A' or 'Training B' on the study laptop, which conceals whether the procedure is AR or PT. These folders were labelled by an independent researcher prior to the start of the trial. Thus the participants, therapists and study staff will be blinded to allocation, to minimize the risk of bias.

#### Measures

Table 1 displays the treatment and measurement plan for the study. The measures consist of the following:

- A baseline questionnaire to collect information on the demographic and clinical characteristics of participants. Participant age, gender, ethnicity, education and employment status are classified using UK Census 2011 categories [40]. The questionnaire also contains information on smoking history including the Fagerström Test of Nicotine Dependence (FTND) [41], a 6-item measure assessing the severity of nicotine dependence.
- A visual probe task and pictorial Stroop task to assess attentional bias.
- The Mood and Physical Symptoms Scale (MPSS) [42]. This will be administered at the beginning of every session to assess urge to smoke and withdrawal. A modified version of the MPSS will be used in which each of the nine items is rated on a scale from 1–7. Items relating to the strength and frequency of urges can be combined to produce a composite score (MPSS-C); this is also the case for combined mood items (MPSS-M). The MPSS was preferred over other measures such as the Questionnaire of Smoking Urges because of its superiority in predicting treatment outcomes [43,44].
- Exhaled carbon monoxide (CO). Readings will be taken at the beginning of each session to biochemically verify smoking status.
- A visual analogue scale (VAS) to measure cue-induced craving at the beginning of the second session and following attentional bias assessments. Measurements will be recorded on a 100 mm scale from "Not At All" to "Extremely" prior to and after the task.

- Ecological Momentary Assessment (EMA) [45] to collect information on lapses. EMA is an approach to collecting data in real-time on hand-held electronic devices; it does not carry the risk of recall bias like paper diaries [46]. Participants will be given an electronic diary at the first session and they will be instructed to record any lapses that occur and the circumstances in which the lapse occurs up to 5 weeks post quit day. Those who use an electronic diary will be paid up to £75 at the 8-week session for completing assessments in this way.
- A questionnaire on knowledge of group allocation.
- A patient satisfaction questionnaire developed by the study team on the acceptability of the training tasks. Two items relate to how difficult the task is to understand and carry out, while a further two items assess the convenience of task. Items are rated on a 5-point scale ranging from "not at all difficult" to "extremely difficult" and "very convenient" to "very inconvenient".

#### Materials

Eighteen picture pairs of smoking-related and matched neutral pictures will be used across attentional bias assessment and training tasks (picture pairs 1–18). These stimuli have been tested and applied in previous research [47,48]. Each set of pictures consists of a colour photograph of a smoking-related stimulus or scene (e.g. a close-up of a cigarette) matched on age, sex, complexity and ethnicity to another photograph containing no smoking-related content. In the assessment version of the visual probe task and pictorial Stroop task, 12 picture pairs will be used (picture pairs 1–12). Similarly in the AR and PT versions of the visual probe task, the 12 picture pairs consist of 6 picture pairs featured in the assessment version of the task (picture pairs 6–12) in addition to 6 new picture pairs (picture pairs 13–18). An extra 4 neutral picture pairs will be used for practice trials before each task.

#### Clinic Tasks

- Visual probe task  
At the baseline session and again at 4 weeks post-quit, 8 weeks, 3 months and 6 months, all participants complete the assessment version of the visual probe task. The assessment version, which will be used to measure attentional bias, comprises a total of 192 trials, presented in two blocks. Each trial begins with a fixation cross displayed in the centre of the computer screen for 500 ms. A picture pair of smoking-related and neutral pictures is then presented side-by-side on the screen for 500 ms. After this picture pair



**Table 1 Treatment and assessment schedule**

Session	Treatment	Measures
Baseline (week -2)	Withdrawal-oriented behavioural support	<ul style="list-style-type: none"> <li>• Baseline questionnaire (demographics, smoking history, Fagerstrom Test for Nicotine Dependence (FTND))</li> <li>• Mood and Physical Symptoms Scale (MPSS)</li> <li>• Exhaled carbon monoxide (CO)</li> <li>• Attentional bias assessment (visual probe and Stroop tasks)</li> </ul>
Pre-quit visit (week -1) Randomisation week	1 week supply nicotine patches Withdrawal-oriented behavioural support Intervention group receives attentional retraining (AR). Control group receives placebo training (PT)	<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• VAS measure of craving (pre &amp; post cue exposure task)</li> </ul>
Quit day (week 0)	1 week supply nicotine patches Withdrawal-oriented behavioural support Intervention group receives AR. Control group receives PT	<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> </ul>
Post-quit visits (weeks +1, +2, +3)	1 week supply nicotine patches Withdrawal-oriented behavioural support Intervention group receives AR. Control group receives PT	<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• Lapses recorded on electronic diary</li> </ul>
Week +4 post-quit visit	4 week supply nicotine patches Withdrawal-oriented behavioural support	<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• Attentional bias assessment (visual probe and Stroop tasks)</li> <li>• VAS measure of craving (pre &amp; post cue exposure task)</li> <li>• Group allocation assessment</li> <li>• Lapses recorded on electronic diary (up to +5 weeks) thereafter reported in clinic CRF</li> </ul>
Week +8 post-quit visit	4 week supply transdermal nicotine patches (where eligible)	<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• Attentional bias assessment (visual probe and Stroop tasks)</li> <li>• VAS measure of craving (pre &amp; post cue exposure task)</li> <li>• Lapses reported in clinic CRF</li> </ul>
3 months post-quit visit		<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• Attentional bias assessment (visual probe and Stroop tasks)</li> <li>• VAS measure of craving (pre &amp; post cue exposure task)</li> <li>• Lapses reported in clinic CRF</li> </ul>
6 months post-quit visit		<ul style="list-style-type: none"> <li>• CO</li> <li>• MPSS</li> <li>• Attentional bias assessment (visual probe and pictorial Stroop task)</li> <li>• VAS measure of craving (pre &amp; post cue exposure task)</li> <li>• Lapses reported in clinic CRF</li> <li>• Patient satisfaction questionnaire</li> </ul>

disappears, a visual probe is presented in the location formerly occupied by one of the pictures. This probe is either a circle or square. Participants are required to discriminate the identity of the probe and respond accordingly by pressing the up or down arrow keys on the keyboard as quickly as possible. There is a 500 ms interval before the next trial. Presentation of each picture-pair and probe location is counterbalanced. In all trials, the visual probe replaces the smoking-related and neutral pictures with equal frequency. At the start of the task, participants carry out 8 practice trials in which neutral picture pairs are presented first, to allow them to become familiar with the procedure. Each block of trials is presented in a new random order for each participant, using EPrime version 2 (Psychology Software Tools Inc., Pittsburgh PA). The task takes approximately 16 minutes. Attentional bias scores will be calculated from

reaction time (RT) data; an attentional bias towards smoking cues is characterized by faster reaction times towards smoking-related pictures than neutral pictures.

- **Pictorial Stroop task**

All participants will carry out a pictorial Stroop task as an additional measure of cognitive bias. The pictorial Stroop task will be given after the visual probe task at the baseline session and again at 4 weeks post-quit, 8 weeks, 3 months and 6 months. The task comprises a total of 192 trials, presented in four blocks of 48 trials, with each block consisting of smoking-related pictures or neutral pictures only. Each picture is presented centrally on a computer screen with either an outline of a red, blue, yellow or green border. Participants are required to indicate the colour of the border, while ignoring the picture, by pressing one of four corresponding labelled keys on the keyboard, as quickly as possible. Participants

receive 8 practice trials in which neutral pictures are presented first, to allow them to become familiar with the procedure. A short break between blocks will be permitted.

Each block of trials is presented in a new random order for each participant, using EPrime version 2 (Psychology Software Tools Inc., Pittsburgh PA). The task takes approximately 12 minutes to complete. Stroop bias scores will be calculated from RT data; selective processing of smoking cues is characterized by slower reaction times towards smoking-related pictures than neutral pictures.

- **Cue exposure task**

At 1 week prior to quit day, 4 weeks post-quit and follow-up sessions at 8 weeks, 3 months and 6 months, participants in both groups will be given a cue exposure procedure to measure cue-induced craving immediately after completion of the visual probe task and pictorial Stroop task. This is a common procedure in cue-reactivity research [49,50]. Showing a strong craving response to cue-exposure has been shown to predict relapse risk [51]. Prior to attending the session at week -1, participants will be instructed to abstain from smoking for at least 1 hour. We chose an abstinence period of 1 hour to avoid floor effects in craving ratings, commonly found immediately after smoking [52].

In order to standardize the procedure, instructions for the cue exposure task will be recorded on a digital recorder and then played to participants in the relevant clinic sessions. Before the instructions are played, participants will provide a single rating of their urge to smoke on the VAS. The therapist will place a box that conceals a cigarette and a lighter in front of the participant. The recording will then be played, which instructs the participant to lift up the box and handle the cigarette and lighter contained within. The task lasts 3 minutes. Following the task, participants will provide another rating of their urge to smoke on the VAS.

#### **Control group**

Participants allocated to the control group will carry out 5 weekly sessions of PT, starting 1 week prior to their designated quit day. During each session, participants perform 8 practice trials of neutral picture pairs followed by 192 trials of PT, presented in a block of two. Between each block, participants are permitted to have a short break if required. The task takes approximately 16 minutes to complete. On each PT trial, the visual probes always replace smoking-related and neutral pictures with equal frequency.

#### **Intervention group**

Participants allocated to the AR group will carry out 5 weekly sessions of the modified visual probe task, AR, starting 1 week prior to their designated quit day. Eight practice trials of neutral picture pairs are presented prior to the first block of AR trials. A total of 192 training trials are presented in a block of two, where participants have the opportunity to have a break in between. The task takes approximately 16 minutes to complete.

The AR program differs from the PT program only in the location of the visual probes. During each training trial, visual probes always appear in the location of the neutral pictures. Thus, participants always have their attention directed away from smoking-related pictures.

#### **Stop smoking treatment**

Systematic reviews have shown that some behavioural and pharmacological interventions increase people's chances of successfully stopping smoking [53,54]. All participants will therefore be given NRT and receive standard withdrawal orientated behavioural support [38].

Participants in this trial will be offered 21 mg/24 hour nicotine patches as the only choice of treatment. This is because:

- 1) All participants will be regular smokers for whom the 21 mg dose is deemed appropriate.
- 2) The study aims to examine the effects of AR on urge to smoke. Short-acting NRT e.g. inhalator or gum affect cue-induced urges to smoke and reduce their intensity [55]. It would thus be difficult to assess the effects of the AR if short-acting NRT is used. Participants are also not permitted to use varenicline for the same reason [56]. Investigators have found that nicotine patches do not protect against cue-induced craving [57], therefore we consider that patch-use is unlikely to mask the potential effects of retraining.
- 3) The patch is the best tolerated form of NRT and has the highest adherence [58,59].

#### **Dose alteration procedure**

Nicotine patches are well tolerated in the large majority of regular smokers and so we expect that most people will continue with the standard dose. However, there are circumstances when the form or dose of the preparation needs to be changed. This variation reflects pragmatic behaviour in the NHS SSS and is expected to be equal in both arms. We anticipate the following occurrences:

- 1) Minor skin irritation to the patch is one of the most common problems with use. This is commonly eased by swapping from one form of patch to

another, because it is usually intolerance to the glue. If the skin reaction is worse, such as causing blisters that cannot be remedied by emollients and hydrocortisone cream, patch use will be stopped and the participant will be swapped to an equivalent dose of oral NRT.

- 2) Sleep disturbance or vivid dreaming is also one of the most common problems with use of the nicotine patch. This can usually be eased by removing the nicotine patch an hour or so before bedtime and so this will be advised. There is no good evidence that 16 hour patch use is less effective than 24 hour patch use.
- 3) Possible symptoms that dose is too high are uncommon problems, but possible. Nausea is the earliest symptom of overdose, but it is also a common symptom experienced by people often enough. Nicotine has a short half life, meaning that by about 10 hours after first applying a patch, nicotine has reached a steady state. Therefore nausea occurring for the first time days after starting treatment is unlikely to be due to the patch. More definite symptoms are as follows, muscular twitching, dizziness, confusion, rapid pounding heart, high blood pressure, vomiting, and weakness. However, 21 mg/24 hour patch systems come as 14 mg/24 hours and 7 mg/24 hours, which can be used in a step down system. If the therapist thinks that an overdose is likely, the precaution will be to step down the dose to the next step i.e. from 21 mg to 14 mg, or from 14 mg to 7 mg.

#### Duration of treatment and instructions for use

Treatment with NRT will start either on the evening prior to quit day or the morning of quit day, depending on personal preference. Patches will be dispensed accordingly during the second visit, which is 1 week prior to quit day. Instructions for patch use include changing it every 24 hours, using a different area of skin for the new patch. Participants will be advised to continue using the patch for at least 8 weeks or stop if they abandon their quit attempt before the 8 weeks. The therapist in consultation with the patient may choose to step down the patch as discussed above. Step down is not necessary as there is no evidence to suggest that it enhances efficacy, but it is commonly perceived as helpful by patients. Step down towards the end of treatment will not be permitted to commence until at least 4 weeks after quit day. The therapist will be instructed not to suggest stepping down in people who have had recent lapses. Some organisations we are working with do not allow treatment for longer than 8 weeks, but, in those that do, the therapist should consult the participant about longer courses of treatment up to 12 weeks duration. This

decision will be at the discretion of the therapist in consultation with the patient.

Behavioural support will start 2 weeks prior to quit day, and last up to 4 weeks after quit day. This follows the typical 7-session withdrawal orientated therapy programme offered in existing NHS SSS [38].

#### Reporting of adverse events

This is not a trial of an investigational medical product. We are using a licensed medical product within the terms of its license and in accord with clinical guidelines. We therefore expect relatively few problems and so there are no special reporting requirements. The therapist leading the sessions will manage problems within his/her own competence. Clinical advice will be sought from the trial doctor. Between them, the therapist and trial doctor will decide how to manage unexpected problems and whether to report a suspected unexpected serious adverse reaction (SUSAR) to the Medicines and Health Care Regulatory Authority using the yellow card system (this is a standard system for reporting unusual reactions to medication).

However, for the purposes of the trial, we will record clinically significant adverse events that lead to a change in medication management or is considered to be significant otherwise. This will allow us to track changes in medication instruction, such as swapping to 16 hour use or dose alterations. The CRF will be used to record the date, the nature of the adverse event/symptoms, and the action taken.

#### Primary trial outcomes

- Measure of attentional bias during assessment trials of the visual probe task, as measured by the difference in median reaction time (ms) taken to respond to probes replacing smoking-related stimuli versus probes replacing neutral stimuli. This will be assessed at 4 weeks post-quit in abstinent and non-abstinent smokers across both trial arms, following recommendations of Shiffman et al. [60].
- Strength of weekly urge to smoke on the MPSS, measured up to 4 weeks post-quit in abstinent and non-abstinent smokers across both trial arms.

#### Secondary trial outcomes

- Strength of weekly withdrawal symptoms on the MPSS, measured up to 4 weeks post-quit in abstinent and non-abstinent smokers across both trial arms.
- Prolonged abstinence measured and biochemically validated at 4 weeks post-quit and each follow-up



using the Russell standard [39]. Criteria for the Russell standard includes a 2 week grace period from quit day, followed by smoking no more than 5 cigarettes and verification by means of exhaled CO, with a cut-off point of <10 ppm.

- Time to first lapse, with a lapse episode defined here as any smoking, even a puff [39].

#### Other trial outcomes

- Feasibility of running the ARTS trial within NHS SSS assessed on the basis of:
  - Rates of response to patient invitation letters;
  - Rates of recruitment at telephone screening;
  - Rates of attendance at clinic visits;
  - Rates of drop out prior to and after randomisation.
- User acceptability as measured by ratings of perceived usefulness on a patient satisfaction questionnaire.
- Change in cue-induced cravings measured on the VAS prior to and at the end of the cue-exposure task at 4 weeks, 8 weeks, 3 months and 6 months post-quit day in abstinent and non-abstinent smokers across both trial arms.
- Measure of cognitive processing bias on the pictorial Stroop task, to assess generalisation of AR effects at 4 weeks post-quit in abstinent and non-abstinent smokers across both trial arms. Stroop bias will be measured by the difference in median reaction time taken to respond to colour-naming of smoking-related stimuli versus colour-naming of neutral stimuli.
- Measure of attentional bias towards novel untrained stimuli on the visual probe task at 4 weeks post-quit in abstinent and non-abstinent smokers across both trial arms.
- Measure of attentional bias on the visual probe task and pictorial Stroop task at 8 weeks, 3 months and 6 months to assess long term effects of AR.
- Strength of urge to smoke and withdrawal symptoms on the MPSS, measured up to 8 weeks, 3 months and 6 months to assess long term effects of AR.

#### Power calculation

The sample size is based on the following. In these calculations, we assume that only quitters will continue to attend clinic and that the measures will be analysed primarily in abstinent smokers, as is standard practice with withdrawal phenomena [60].

We assume conservatively that the effect of 5 sessions of AR will be no greater than the effect of a single session. From the findings of the Attwood et al.

study [26], to detect a mean reduction of 26 ms (SD = 43 ms) with 80% power and a type 1 error rate of 5%, 42 participants in each group will be required. We revised this calculation to adjust for baseline attentional bias scores. In our pilot study of AR, we found an estimated correlation coefficient of -0.13 between baseline and post-training measurements. Thus, to detect a reduction of 26 ms with the same standard deviation, power and type 1 error stated above, 42 participants are still required in each group. We expect that at least 50% of participants will reach the Russell standard abstinence criteria at 4 weeks, as the NHS services achieve greater than this, providing about 50 abstinent participants in each arm, sufficient to test this hypothesis.

The trial is an exploratory study but is powered to detect differences in urge to smoke. One study on smokers quitting on pharmacotherapy found that the mean change in urge strength between quit day and week 1 was about 0.5 points measured with the MPSS and had a standard deviation of 1.2 [61]. Another study reported that glucose reduced urge strength by 1.0 points, although this was immediately after dosing [62]. In both of these studies, MPSS urge strength was scored 0–5 [42]. We assume that if AR can reduce urge strength by 0.6 points, then 62 participants in each group will be needed to detect this with 80% power and a type 1 error rate of 5%. From the earlier study [61] we used an estimated correlation coefficient of 0.41 between quit day and post-training urge strength to adjust this power calculation. This means that to detect a 0.6 point reduction in urge strength (SD = 1.2) with 80% power and a type 1 error rate of 5%, 53 participants would be required in each group. In the first 4 weeks, when withdrawal is at its height, this implies that about 200 smokers will be needed, assuming that 60% will achieve abstinence in the first 4 weeks.

The trial is not large enough to detect the effects of AR on prolonged abstinence as several hundred participants would be needed. With a sample size of 200 smokers, if AR increased abstinence rates by 30% (RR = 1.3), we have approximately 57% power to detect a difference in the proportion abstinent, using a two-sided test with a type 1 error rate of 5% and assuming an abstinence rate of 50% in the control group.

#### Loss to follow-up

Participants who fail to attend clinic and do not respond to our telephone calls will be classed as smokers for the analysis of smoking abstinence, as is standard [39]. We expect to make contact with more than 90% of people at 6 month follow-up, based on experiences of a recent trial [61]. We anticipate that the effects of AR on attentional bias and withdrawal phenomena will be analysed primarily in abstinent smokers, as recommended by

Shiffman et al. (2004) [60], so defaulting from routine clinic appointments by failed quitters is not considered a threat on the integrity of the trial. We therefore do not require those participants who failed to maintain abstinence and abandoned their quit to continue to attend clinics except for reasons detailed below.

This study could give valuable information on what happens to attentional bias over time, how it is affected by training, how it is affected by resuming smoking, and whether the training effect is contingent on continued abstinence. Accordingly, we will ask all participants regardless of smoking status to attend the follow-up visits. Adequate compensation should increase the likelihood of attendance.

#### Analysis

- Primary analyses

Attentional bias scores on the visual probe task will be calculated by subtracting median RTs to probes that replace smoking-related pictures from median RTs to probes that replace neutral pictures, with positive scores indicating a bias towards smoking cues and negative scores indicating a bias towards neutral cues. Median RTs will be used because distributions of mean RTs are often reported as skewed [33,63]; therefore we do not need to set parameters for outlying RTs. Bias scores, as measured at 4 weeks post-quit, will be used to examine AR effects on attentional bias firstly by trial arm and secondly by abstinence status using ANCOVA. An alpha level of 0.05 will be used. These analyses will be performed using PASW Statistics 18 (SPSS, Inc., 2009, Chicago, IL, USA).

To investigate AR effects on weekly urge to smoke, data will be analysed using a mixed effects regression model with an autoregressive variance-covariance structure, to allow for variations in craving between participants. This will enable all weekly time points to be included and modelled simultaneously. An autoregressive modelling structure takes into consideration that repeated craving measurements taken closer together in time on the same participant are likely to be more highly correlated than measurements that are taken further apart in time [64]. This modelling technique will be used for MPSS composite scores for urge to smoke (MPSS-C). Regression coefficients, p-values and 95% confidence intervals (CI) will be derived from the models. These analyses will be undertaken using Stata 12.0 (StataCorp, 2011, College Station, TX: StataCorp LP).

Intention-to-treat analyses will be performed to account for people who drop out of treatment.

- Secondary analyses

Effects of AR on withdrawal will be examined using the same technique stated for urge to smoke analyses, in a mixed effects regression model of composite scores for withdrawal symptoms (MPSS-M). We will control for baseline MPSS-M scores, as is standard for the MPSS [42].

To determine the proportion of people achieving abstinence by trial arm, risk ratios (RRs) will be calculated with corresponding 95% CIs. Those reported as lost-to-follow up will be counted as non-abstinent, as is standard in the reporting of smoking cessation trials [39,65].

Proportional hazards modelling will be used to analyse the median time to lapse by trial arm; hazard ratios (HRs) will be reported with corresponding 95% CIs. These analyses will be performed using Stata 12.0 (StataCorp, 2011, College Station, TX: StataCorp LP).

- Additional analyses

We will adjust analyses of attentional bias scores, MPSS-C scores and MPSS-M scores for potential moderators of attentional bias, urge to smoke and withdrawal symptoms. These will include age, gender and FTND across all analyses. Pre-quit urge to smoke will also be examined in the model of attentional bias scores and pre-quit attentional bias in the models of MPSS-C and MPSS-M.

To investigate longer-term retraining effects, we will analyse 8 week, 3 month and 6 month post-quit data for attentional bias scores using ANCOVA and mixed-effects regression models for MPSS-C scores and MPSS-M scores, as stated previously.

To examine AR effects on cue-induced craving, VAS scores will be analysed in the same way as MPSS-C and MPSS-M scores, in mixed-effects regression models. Visual analogue scale scores will be calculated from measurements taken from a 0–100 mm scale before and after the cue exposure task, which are administered 1 week before quit day and again at 4 weeks, 8 weeks and 3 months post-quit. The difference between pre and post measurements will be calculated and the change in cue-induced craving over time will be reported. Generalisation of AR to other cognitive bias measures will be assessed using RT scores from the pictorial Stroop task. Stroop bias scores will be calculated by subtracting median RTs to probes that replace neutral pictures from median RTs to probes that replace smoking-related pictures. Slower RTs towards smoking-related pictures indicate a bias towards smoking cues. Again, parameters for outlying RTs do not need to be defined as median rather than mean RTs will be used. Bias scores, as measured at

4 weeks post-quit, will be used to examine AR effects on Stroop bias firstly by trial arm and secondly by abstinence status using ANCOVA.

Similarly, we will assess whether AR generalises to untrained novel stimuli that only appear in the assessment versions of the visual probe task and not during training sessions. Attentional bias scores for the trained and untrained stimuli will therefore be analysed separately using ANCOVAs.

Responses to the patient satisfaction questionnaire and identification of group allocation will be compared across trial arms as percentages.

#### Ethics and research governance

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the ICH-GCP, the EU Clinical Trials Directive and all applicable regulatory requirements. The study protocol and other documentation were approved by the National Research Ethics Committee (10/H1206/34) and local NHS Research & Development offices. Subsequent protocol amendments will be submitted to the Research Ethics Committee for approval, and the other bodies where necessary. We will provide the Research Ethics Committee with annual progress reports, in addition to a final study report.

#### Discussion

This is the first trial to assess the potential clinical translation of AR procedures in smokers attempting to quit using NHS SSS. Multiple sessions of AR might increase treatment efficacy on top of standard treatment, as demonstrated in a recent trial of alcohol-dependent patients [33]. If effective, not only could AR be used in stop smoking clinics, it could also be offered as a web-based intervention on NHS stop smoking websites as another potentially low-cost alternative.

Several procedures are in place to minimise potential sources of bias. To minimise the risk of selection bias, we are using a simple random sequence for assigning participants to groups. To minimise performance bias, we are blinding all therapists and participants to group allocation, though there is a risk of participants becoming aware of which group they have been assigned to while carrying out the task itself. At follow up, we will assess participants' knowledge of which intervention they believe to have received.

While this trial offers the ability to examine AR as a therapeutic tool, data on attentional bias and its relation to urges to smoke, cue-induced cravings and resumption of smoking will enhance our understanding of relapse and possible preventative strategies. Knowing how urges to smoke strike, their antecedents and smoker's responses to these are a key part of designing future intervention strategies.

#### Competing interests

RH, LN, MAM, RH, SS, SSu and SGF have no competing interests. PA has done research and consultancy for manufacturers of smoking cessation medication.

#### Authors' contributions

MRM and PA conceived the study. RH, PA, MRM, SS, RH and SSu were involved in the initial discussions that led to the grant application and writing of the study protocol. RH, PA, MRM, SS, SGF and SSu participated in the study design. RH is the trial statistician and together with LN, MAM, PA and RH devised the statistical analysis plan. All authors contributed to the draft of the manuscript. All authors read and approved the final version of the manuscript.

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## Appendix 11. GP practice invitation letter to participants

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Participant Invitation Letter v.1, 15.03.10

[GP letterhead]

Date ....../....../....

Patient X  
X Street  
X Town  
X County  
XXXX XXX

Dear Mr/Ms. X,

**Are you thinking of stopping smoking but concerned about whether you can keep it up?**

I am writing to you because our records show that you are currently smoking. Stopping smoking would probably make you feel better and would greatly reduce your chance of getting heart disease and cancer in the future. However, many people have genuine concerns about staying quit once they attempt to quit smoking. A research group from the University of Birmingham have asked us to invite you to take part in a research study looking at ways of increasing your chances of staying quit. In the study, you would get high quality support and advice about how to stop smoking. You would also receive support during you quit, which would include using a new computer programme while using nicotine replacement therapy (NRT) patches.

This surgery has agreed to write to patients who might be interested in taking part in this study, which will take place at or close to the surgery. If you still smoke and want to stop, joining this study would give you a really good chance of success. The study would involve you making regular visits to the research clinic for advice and support in stopping smoking and taking part in a computer-based task. You will be given a course of NRT to assist you in your quit attempt. You would also be required to provide a carbon monoxide reading and fill in some short questionnaires at each visit.

If you want to take part or want to know more about the study, please call the trial coordinator, Miss Sarah Clarke, on 0121 414 3027 or send an email to [s.clarke.2@bham.ac.uk](mailto:s.clarke.2@bham.ac.uk). Alternatively you may call or text your name to 07845 877 993 and the trial coordinator will

call you by the next working day. If you don't want to join the study but do want to quit smoking, please contact the surgery anyway.

We try to keep your medical records up to date at this surgery. If you have stopped smoking already, please ring XX on XX and we will update our records.

Many thanks,

Yours sincerely,

Dr. X

## Appendix 12. Patient information sheet

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient Information Sheet , v5, 17/03/11



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### **If you are a smoker wanting to quit, we are inviting you to take part in a research study.**

Stopping smoking is one of the quickest ways to improve your health and could lead to you feeling better. We would like to invite you to take part in a study that may help you stop smoking and increase your chances of staying quit. We would like you to attend appointments at your GP surgery where you will take part in a computer-based task at each appointment and receive help and support in your quit attempt with a stop smoking advisor. You will also be given nicotine replacement therapy (NRT) in the form of patches, which is offered routinely by the NHS Stop Smoking Services. We will also give you an electronic diary to take away with you, which will ask you to record how you are feeling throughout the day. On your second visit and final visit, you will be asked to handle a cigarette without lighting it, as a way of telling how much progress you have made during your quit attempt.

Before you decide *whether to take part* it is important for you to take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What is the purpose of the study?**

Over 75% of initially successful quitters go back to smoking within a year. One possible reason why people start smoking again may be because the sight or smell of a cigarette or a particular place reminds them of smoking. We call these 'triggers'. Previous research has shown that smokers have what is known as an 'attentional bias', where they tend to pay more attention to these triggers related to smoking. This could create the urge to start smoking again and at the moment there are few successful treatments to help people resist the urge from smoking again.

Researchers at the University of Birmingham, University of Bristol, University of Cambridge and University of Pittsburgh have developed a computer training package that might help people cope with these triggers, while they attempt to stop smoking. We would like to use this computer training package alongside the standard care offered by the NHS stop smoking services, to help people in their attempt to stop smoking.

#### **Why have I been chosen?**

You are a smoker wanting to stop smoking and have responded to a letter sent from your GP practice, inviting you to participate in the study.

#### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep, you will be asked to sign a consent form and you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Your GP will also be informed of your participation in the study.

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient Information Sheet , v5, 17/03/11

**What will happen to me if I take part and what do I have to do?**

If you choose to take part in the study, you will be invited to attend a seven-session weekly NHS stop smoking clinic at your GP surgery. Sometimes we don't know which way of treating patients is best. To find out, we need to compare treatments. We will therefore put people into groups: one group will complete a computer task with training and the other group will complete a computer task without training. The results will be compared to see if there is a difference between the two. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). You will have a 50/50 chance of being in the group that completes the computer task with the training. This is also a 'double blind trial', which means neither you, your stop smoking advisor or the researchers involved will know which group you are in until the end of the study.

**Session 1**

A member of the research team will talk to you about the study and ask you for your consent to take part. If you agree to take part, you will be asked to provide an exhaled carbon monoxide reading, fill in a short questionnaire and take part in a series of computer tasks that will take no longer than 30 minutes to complete. During the session you will also be trained to use an electronic diary to take away with you. The diary will beep at random times during the day to record how you are feeling while you are still smoking. We would like you to complete these diary entries as honestly and accurately as you can. The diary entries you make will be sent back electronically to the research team at the University of Birmingham. You will be asked to use the diary for seven days and bring it to your next session. You will be smoking as normal between this session and the next.

**Session 2**

We will ask you to come to this session without having smoked a cigarette for at least 1 hour. If you have managed to use the electronic diary successfully and without any difficulties, you will be randomly allocated to one of the two groups. If you have not managed to fill in your diary entries you will be given the number of the local Stop Smoking Service and will not continue on in the study.

If you remain in the study you will be asked to provide a carbon monoxide reading and fill in a short questionnaire. As a way of looking at your progress during your quit attempt, you will be given the task of holding an unlit cigarette at this session and on your final sessions. You will be asked to hold the unlit cigarette for three minutes, after which you will be asked a question on how it makes you feel. Your advisor will support and advise you after this task.

You will also start the computer-based task either with or without training, depending on which group you are in. Your stop smoking advisor will help prepare you for stopping smoking. You will be expected to attempt to quit one week later. You will be given a supply of NRT which you will start using either on the evening before your quit day or on the morning of your quit day. We would like you to continue to use the electronic diary in the following week.

**Session 3**

This will be your quit day. Your advisor will talk to you about your progress and provide advice and support. You will be asked to provide a carbon monoxide reading, fill in a short questionnaire and carry out the computer task with or without training. We would like you to continue to use the electronic diary in the following week.

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient Information Sheet , v5, 17/03/11

#### **Session 4 -6**

At weekly intervals there will be three more sessions with your stop smoking advisor. The main aim of these sessions is to support you in your attempt to stop smoking. At each session, you will receive your NRT supply for the following week. You will be asked to provide a carbon monoxide reading, fill in a short questionnaire and carry out the computer task with or without training. Session 6 is the last time you will carry out the computer task with or without training. We would like you to continue to use the electronic diary in the weeks between these sessions.

#### **Session 7**

This will be your last weekly session and will be four weeks after you quit smoking. You will be given enough NRT to last until the 8 week follow-up to help you continue with your quit attempt. You will be asked to provide a carbon monoxide reading, fill in some short questionnaires and take part in a series of computer tasks.

You will again be given the task of holding an unlit cigarette for three minutes, after which you will be asked a question on how it makes you feel. Your advisor will support and advise you after this task.

We would like you to continue to use the electronic diary for a further one week.

#### **Session 8 then at 3 and 6 months from quit day**

You will be able to discuss your progress with your advisor. At each session, you will be asked to provide a carbon monoxide reading, fill in some short questionnaires and take part in a series of computer tasks.

You will again be given the task of holding an unlit cigarette for three minutes, after which you will be asked a question on how it makes you feel. Your advisor will support and advise you after this task.

#### **Expenses and payments**

As a thank you for using the electronic diary, you will receive £75 when you return the diary at the 8 week follow-up session. But, if you only complete the diary entries for less than 60% of the time over the 8 weeks that you used it for, you will only receive £40. You will receive a payment of £15 at the 3-month follow-up session and £15 again at the 6-month follow up session as reimbursement for your travel expenses to the clinic.

#### **What are the possible disadvantages and risks of taking part?**

It will take you about 20-30 minutes of your time to complete the computer tasks and you may experience some boredom or tiredness whilst doing this.

#### **What are the possible benefits of taking part in this study?**

Nicotine replacement therapy helps to treat smoking addiction and so it may help you in your attempt to stop smoking. If you are in the group that complete the computer task with training, it may help you stay successful in your attempt to stop smoking; however whether it will do so or not is unknown. We cannot promise that the study will help you but the information we get from this study will help improve the treatment of people who are trying to stop smoking and want to stay quit. The findings from the study might help in developing better stop smoking services in the future.

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient Information Sheet , v5, 17/03/11

**What happens if something goes wrong?**

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms should be available to you. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you from each session will have your name and address removed so that you cannot be recognised from it. All information will be kept in a locked cabinet in a locked room at the University of Birmingham, at all times.

**What will happen to the results of this study?**

We intend to publish the results in a report. You will not be identified in any report/publication.

**Who is organising and funding the research?**

The National Institute for Health Research (NIHR) is funding the work. The study is being run by researchers from the University of Birmingham, University of Bristol, University of Cambridge and University of Pittsburgh. The study is taking place in Birmingham.

**Contact for further information**

We hope that this leaflet answers some of the questions you might have. If you have any problems or questions about this study or your rights as a patient in clinical research, please contact:

Miss Rachna Begh (Chief Investigator)

[Redacted contact information for Miss Rachna Begh]

Dr Paul Aveyard (Principal Investigator)

[Redacted contact information for Dr Paul Aveyard]

### Appendix 13. Telephone screening form for eligibility into the ARTS trial

ARTS Screening form

Dates	Answers	If able to continue in study ask for personal details	
Today's date		Title	
Date of contact		First Name	
Who made contact (person who first mentioned study)		Last Name	
Which surgery?		Address	
Date of initial contact if email		Postcode	
Date of initial contact if letter		Daytime phone	
Do you agree to?		evening phone	
Having answers recorded?		Mobile number	
Being asked questions about your health?		email address	
Smoking related questions.		Surgery for booking	
Are you over 18 years of age? D.O.B?		appointment time	
Do you smoke 10 or more manufactured cigarettes per day OR 12.5g or more tobacco for roll-ups?		appointment day	
Have normal to corrective normal vision?		appointment date	
Are you happy to use nicotine replacement therapy?		comments	
Happy to use an electronic diary?		Sent PIS and appointment letter?	
Not taking part in any medicinal trials and has not done so in the last 3 months?			
Other health questions.			
Can read/fill in questionnaires?			
Currently pregnant or planning on pregnancy?			
Able to do computerised tasks - See computerised images properly and press keyboard buttons?		Person completing data	
Booking Appointment			
Booked or not booked			
Give Reason for not booking: eg: inconvenient clinic times, can't do 7 weeks consecutively (apart from the odd week), has already stopped smoking too little, medical contraindications, patches give problems, only wants Champix			



## Appendix 14. Patient consent form for the ARTS trial

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Consent Form v.5, 17/03/11



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Participant ID: .....

### CONSENT FORM

There are three copies of this form: one for you to keep, one for the study records and one for your patient records.

Title of Study                      ARTS Study

Principal Researcher      Rachna Begh

Please initial box

1. I confirm that I have read and understand the information sheet (version 5, 17/03/11) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I can withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I agree to take part in the above study. ☐
3. I understand that sections of my medical notes may be looked at by members of the project research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I give consent for my General Practitioner (G.P.) to be notified of my participation in the study. ☐
5. I understand that personal information, such as my name and telephone number will be collected by the research team at The University of Birmingham as part of the research and they may need to contact me directly during the study. I understand they will keep this confidential within the research team. ☐
6. I understand that data collected about me for this project will be held under the provisions of the 1998 Data Protection Act and will be stored in manual and/or electronic files in a secure encoded format. ☐
7. I agree to the use of my anonymised data in reports and publications of the study. ☐

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Person taking consent  
(if different from researcher)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

THANK YOU FOR PARTICIPATING IN THIS RESEARCH



**Appendix 15. Clinical procedure for ARTS trial**

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# ARTS STUDY

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# Clinical Procedure

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A double blind randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). This document outlines the study procedures from the initial approach to the final assessment session.

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## **Recruitment**

### **Summary of recruitment process**

1	Brief patient about ARTS and study procedures
2	Check eligibility (pg 3-4 of CRF)
3	Medical History Form (pg 5 of CRF)
4	Concomitant medication form (pg 6 of CRF)
3	Consent Form (in folder)
4	Patient Information Form (in folder)
5	Proceed to first session

## **Recruitment**

Participating practices will write to patients on their list who meet the eligibility criteria inviting them to take part in the study. Those who are interested will call the trial coordinator, who will give them a summary of what the trial involves and run a quick screening checklist. Those who are happy to go ahead will be book an appointment to see one of the trial nurses and a patient information sheet will be posted out.

1. The potential patient will already have read the patient information sheet. Brief the patient about the study and procedures working through the information sheet.
2. If they are still interested check their eligibility using the CRF. Every patient will have a CRF. The study will be recruiting current smokers who
  1. Male or female aged 18 years or over.
  2. Smokes at least 10 cigarettes per day or has a value of 10 parts per million (ppm) for exhaled carbon monoxide (CO).
  3. Have normal or corrected-to-normal vision.
  4. Show evidence of a signed and dated informed consent document indicating that s/he has been informed of all aspects of the study and consents to participate and be randomised to either group.
  5. Be able and willing to complete all study procedures.

Smokers are **non-eligible** if they:

1. A medical condition that prevents them seeing the computerised images properly, attending to the task, or pressing the keyboard

- buttons on the computer accurately, or completing any other study procedures.
2. Are currently using other nicotine replacement therapy (NRT), bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture) that they are not willing to cease using to use study medication.
  3. Have taken part in other medicinal trials in the last 3 months or are doing so during study participation.
  4. Have previously had severe skin reactions to nicotine patches or severe eczema or other skin diseases that make patch use hazardous or undesirable.
  5. Severe acute or chronic medical or psychiatric condition or previously diagnosed clinically important renal or hepatic disease, which may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Check that the main inclusion / exclusion criteria are met by assessment form on pages 3 to 4 of the CRF.

#### **Note**

If the criteria are not met then give the patient an explanation of why we are unable to include them in the study and refer them on to their local stop smoking service. Send the incomplete CRF to the trial manager so we can keep a log of numbers of patients seen but not recruited.

3. Fill in the medical history form on page 5 of the CRF.
4. Fill in the concomitant medication form on page 6 of the CRF.
5. If eligibility criteria are met and the patients decide to progress ask them to read, sign and date the informed consent form. This is completed **in triplicate**; one copy goes to the patient, one sent to the research team and one to be kept in case file at the Practice.

#### **Note**

If the patient **does not** wish to provide consent, send the CRF without smokers contact details to the trial manager so the research team can keep a log of number of patients seen but not recruited.

6. Fill in the patient information form.

7. Provided the individual is happy to do so, proceed with the first session.

### **Session 1**

-2 weeks (pre-quit)

#### **Summary of session 1**

1	Stop smoking support: Contact 1 (No NRT to be given on this day)
2	Patient fills ARTS study baseline questionnaire, week -2 (in folder)
3	Fill in the first part of Visit 1 CRF (pg 7)
3	Visual probe task (on laptop)
4	Explain and issue electronic diary
5	Pictorial Stroop task (on laptop)
6	Book next appointment (ARTS online system)
7	Data entry of Baseline CRF (Baseline visit 1 on ARTS online system)

1. Carry out first session of the stop smoking programme. Carbon monoxide monitoring begins in this session and will be recorded at each visit during the trial. During this session a quit date must be set for two weeks time. No NRTs to be given on this day.
  - Introduce stop smoking programme
  - Fill in stop smoking registration form
  - CO monitoring: Ask the patient to provide a carbon monoxide reading. Refer to CO monitors instructions for correct use. Allow the patients a couple of attempts if practice is needed.
  - Discuss NRTs (in particular the nicotine patch which will be used in the trial)
  - Set quit date
2. Give the patient the baseline questionnaire to fill (ARTS study baseline questionnaire week -2)

3. Visual probe task on the laptop. Refer to visual probe task guide Appendix 1.

The patient has the opportunity to do a practice version of the task which is in the 'Practice visual probe task' folder. For the practice version, enter the subject number as 0, as data from the practice version is not required. The practice version is continuous, so you will have to abort the task for the patient when they are happy to do the real visual probe task.

To abort the practice task, press the control, alt and shift key at the same time.

Continue on to setting up the visual probe task (Appendix 1). There is a break after 8 minutes of the task should the patient need one. This task is expected to take 16 minutes in total.

4. Talk to the patient about the electronic diary. Refer to Appendix xx for guidance in setting up the electronic diary and play the video file named 'Electronic diary instructions' on the laptop. While the video is playing, turn the diary on and follow the instructions on the screen. Give the patient the electronic diary, a charger and a copy of the ARTS instruction booklet. The patient will have to sign a contract on the diary on receipt of the diary. The contract 'ARTS electronic diary sign out form' will be in your resource pack. Keep a log of this on the ARTS electronic diary tracking form (also in your resource pack).

5. Pictorial Stroop task on the laptop. Refer to pictorial Stroop task guide Appendix 2.

Again, there is a practice version of the task in the 'Practice Stroop task' folder if the patient requires a practice-run (you will have to abort this task using the same procedure above). Run the Pictorial Stroop task. There are three breaks during the task should the patient need them. This task is expected to take approximately 12 minutes in total.

6. Book the next appointment for one week's time using the ARTS online system and print this out for patient. Patients need to come to the next session without having smoked for at least an hour. Find out from the patient their preferred way of being sent reminders about appointments (text, email or phone call).
7. Log on to the ARTS online system and enter CRF data (named baseline visit 1) <https://www.pc-crtu.bham.ac.uk/ARTS/>

## Session 2

-1 week (pre-quit)

### Summary of session 2

1	Complete the next section of the CRF (pg 8)
2	Upload data from electronic diary
3	Patient fills ARTS study questionnaire, week -1 (in folder)
4	Cue exposure task
5	Carry out randomisation on ARTS online system
6	Training - Part 1
7	Behavioural support (one week supply of NRT to be given on this day in preparation for quit day)
8	Training - Part 2
9	Data entry of CRF on ARTS online system (visit -1)
10	Book next appointment

1. Complete the next section of the CRF. Page 8, visit 2, -1 week prequit. Confirm consent and ensure that the patient still meets the inclusion criteria.
2. Upload data from the electronic diary using guidelines in Appendix 6. Return the electronic diary to patient. Encourage patient to record all cigarettes they smoke and respond to prompts if compliance is low.
3. Give the patient the ARTS week -1 questionnaire to fill. Patient to fill in questions 1-3 and Time 1 pre cue exposure task question and stop where it says break.
4. Cue exposure task – please refer to cue exposure task guide (Appendix 3). For this task you will have a cigarette, a lighter and a box. Play the sound file named 'Cue exposure voiceover' from the laptop which will give instructions on the task. After the task the patient completes the last page of the questionnaire, Time 2 post cue exposure task question.

5. Log on to the ARTS online system <https://www.pc-crtu.bham.ac.uk/ARTS/> and navigate to the 'Patients' tab and click on 'Randomise'. Find the patient in the list to bring up their details by clicking on 'View'. Click 'Finish' to randomise the patient. The system will indicate whether the patient is randomised to 'Training A' or 'Training B'. Write down which group the patient is randomised to on page 1 of the CRF.

Explain to the patient that they will be randomised in this session. They will either be in the intervention arm and receive attentional bias retraining or be in the control group and receive control training. They will continue to receive behavioural support and nicotine patches regardless of which arm they are randomised to. The patient should be made aware the randomisation process is computerised and that they cannot choose the group they will be allocated to and neither they nor the research team / nurse would know the group they are allocated to.

6. Training part 1

Set up the training for the patient on the laptop. Click on the 'Training A' folder if the patient has been randomised to the group 'Training A' or click on the 'Training B' folder if the patient has been randomised to the group 'Training B'. Refer to the training guide for information on how to run the program (Appendix 4). This will run for about 16 minutes. Training is split into two parts, Part 1 and Part 2. There is a break in between the two parts and this will be indicated on the screen.

7. Provide behavioural support after Part 1 of training.

- Confirm quit date of next week with patient in this session.
- C0 readings taken
- NRT patches to be given in this session.

### **Explain how nicotine patch use works**

"When you smoke, nicotine is absorbed rapidly from the smoke and travels to the brain where it attacks the brain's motivation system. This causes your brain to pay attention to what was happening just before the nicotine got to your brain- which was smoking a cigarette. If you repeat this process, your brain will come to expect it's hit of nicotine in particular times or places when you would usually smoke. This is automatic learning and is nothing to do with what you want to happen or feel. When you try to stop smoking, your brain's motivation system will send a message which you feel as a craving, particularly when you are in places where you would normally have smoked. These cravings can be very strong and they are the main reason people fail to quit smoking in the early days. Eventually they will go away as your brain's motivation forgets, but this can take weeks or months. If you put on a nicotine patch, your cravings will not be

as strong and there is more chance you will be able to avoid smoking. The longer you go without smoking, the more chance you have of making it as a non-smoker. Wearing the patch will help you get there. Does that make sense to you?"

- Encourage and emphasise how important regular use is.
- Dispense one week's worth of medication to start use the day prior to quit day (or from the morning of quit day).
- Give advice on where to put the patch (any area of hairless skin excluding the breasts).
- Ask whether the patient has questions about patch use or NRT and reassure the patient about the use of the patch.

When you are ready, instruct the patient to resume with Part 2 of training on the laptop.

#### 8. Training part 2

Continue with the second part of training on the laptop for patients.

9. Book the next appointment using the ARTS online system and print out for patient.
10. Log on to the ARTS online system and enter CRF data (named visit -1)  
<https://www.pc-crtu.bham.ac.uk/ARTS/>



**Session 3**

0 Week (quit day)

**Summary of session 3**

1	Fill out next section of CRF (pg 9)
2	Patient fills ARTS study questionnaire, week 0 (in folder)
2	Upload data from electronic diary
3	Training - Part 1
4	Behavioural support (One weeks supply of NRT to be given)
5	Training - Part 2
6	Data entry on ARTS online system – week 0
7	Book next appointment

1. Fill out the next section of the CRF, page 9.
2. Upload the data from electronic diary using guidelines in Appendix 6. Encourage patient to use diary if compliance is low.
3. Training part 1
 

Set up the training for the patient on the laptop. Check which group the patient was randomised to (either Training A or Training B) which you wrote down on page 1 of the CRF from the previous session.
4. Provide behavioural support after Part 1 of training.
  - Today is quit day; emphasise the not a puff rule.
  - Check that the participant has their patch on.
  - Check for any concerns and worries about the medication.
  - Emphasise how important regularly using the patch is. If necessary explain how the patch works.
  - It is important the person knows that lapsing is 'not an option', but if they do, it is even more important that s/he uses the patch. Lapsing on

a patch is less likely to lead to relapse and it is perfectly safe to smoke while on a patch.

- CO reading
- Dispense one week's medication.

5. Training part 2

Continue with the second part of training on the laptop for patients

6. Book the next appointment using the ARTS online system and print out for patient.
7. Log on to the ARTS online system and enter CRF data (named visit 0)  
<https://www.pc-crtu.bham.ac.uk/ARTS/>

**Session 4-6**

+1 week, +2 week, +3 weeks post-quit

**Summary of session 4-6**

1	Fill in next session of CRF (session 4 pg. 10, session 5 pg 12, session 6 pg 14)
2	Patient fills ARTS study questionnaire, week +1/week +2/week +3 (in folder)
3	Upload data from electronic diary
4	Training part 1
5	Behavioural support (One weeks supply of NRT to be given)
6	Training part 2
7	Book next appointment
8	Data entry of CRF on ARTS online system

1. Fill out the next section of the CRF - Page 10 for session 4, page 12 for session 5 and page 14 for session 6.
2. Give the patient the appropriate questionnaire to fill (week +1, +2, +3).
3. Upload the data from electronic diary using guidelines in Appendix 6. Encourage patient to use diary if compliance is low.
4. Training part 1  
Set up the training for the patient on the laptop. Check which group the patient was randomised to (either Training A or Training B) which you wrote down on page 1 of the CRF.
5. Behavioural support
  - Check that the participant has their patch on.
  - Check for any concerns and worries about the medication.
  - Emphasise how important regularly using the patch is. If necessary explain how the patch works.

- It is important the person knows that lapsing is 'not an option', but if they do, it is even more important that s/he uses the patch. Lapsing on a patch is less likely to lead to relapse and it is perfectly safe to smoke while on a patch.
- CO reading
- Dispense one week's medication.

If the patient has abandoned their quit attempt, their next visit will be at +12 weeks and +24 weeks follow up sessions. They will need to return the electronic diaries and sign them back in. They will receive £15 on returning the phones if they drop out of the study before visit 8.

6. Training part 2

Continue with the second part of training on the laptop for patients.

7. Book the next appointment using the ARTS online system and print out for patient.

8. Log on to the ARTS online system and enter CRF data

<https://www.pc-crtu.bham.ac.uk/ARTS/>

## Session 7

+4 weeks post quit day

### Summary of session 7

1	Complete the next section of the CRF (pg 16)
2	Patient fills first part of ARTS study questionnaire, week +4 (in folder)
3	Upload data from electronic diary
4	Visual Probe task
5	Behavioural support (Three weeks supply of NRT to be given)
6	Pictorial Stroop task
7	Cue exposure task
8	Book next appointment
9	Data entry of Week +7 CRF on ARTS online system (Visit 7)

1. Complete the next session of the CRF(page 16).
2. Patient fills ARTS week + 4 questionnaire in folder. Patient to fill in questions 1-3 and stop where it says break.
3. Upload the data from electronic diary. The patient will use the dairy for one more week. The next appointment is in four weeks so patient to keep the diary off after one week and return it with the charger at their next appointment in four weeks time.
4. Visual probe task  
To be set up on laptop for patient. There is a break after 8 minutes should the patient need one. This is expected to last for approximately 16 minutes.
5. Behavioural support: this is the final behavioural support session. Give the patients their final set of patches to last them for 4 weeks.
  - Check that the participant has their patch on.
  - Check for any concerns and worries about the medication.

- Emphasise how important regularly using the patch is. If necessary explain how the patch works.
- It is important the person knows that lapsing is 'not an option', but if they do, it is even more important that s/he uses the patch. Lapsing on a patch is less likely to lead to relapse and it is perfectly safe to smoke while on a patch.
- CO reading
- Dispense three week's medication
- Consider whether to reduce the dose of the nicotine patch. If in doubt do not reduce the dose.

6. Pictorial Stroop task

To be set up on laptop for patient. There are three breaks during the task should the patient need them. This task is expected to take approximately 12 minutes in total.

7. Cue exposure task

Patient to return to filling in ARTS week +4 questionnaire, Time 1, pre cue exposure task question. Set up cue exposure task (cigarette, lighter and a box), play the sound file named 'Cue exposure voiceover' from the laptop. After the task, the patient completes the last page of the questionnaire, Time 2 post cue exposure task question.

8. Book next appointment for 4 weeks on ARTS online system.

9. Log on to the ARTS online system and enter CRF data

<https://www.pc-crtu.bham.ac.uk/ARTS/>

**Session 8**

+8 weeks post quit day

**Summary of session 8**

1	Complete first part of CRF (Pg 18)
2	Patient fills ARTS study questionnaire, week +8 (in folder)
3	Visual probe task
4	CO measurement
5	Pictorial Stroop task
6	Cue exposure task
7	Patient fills ARTS patient satisfaction questionnaire (in folder)
8	Upload data from electronic diary, collect electronic diary + make payment
9	Book next appointment for 4 weeks on ARTS online system
10	Data entry of week +8 CRF on ARTS online system

1. Complete first part of CRF (Page 18).
2. Patient fills ARTS week +8 questionnaire. After the first section patient to break for visual probe task (to be set up on laptop).
3. Set up visual probe task on laptop. There is a break after 8 minutes should the patient need one. This is expected to last for approximately 16 minutes.
4. CO measurement.
5. Set up pictorial Stroop task for patient on laptop. There are three breaks during the task should the patient need them. This task is expected to take approximately 12 minutes in total.

6. Patient to refer back to questionnaire and fill in Time 1, pre cue exposure task question. Set up cue exposure task (cigarette, lighter and a box), play the sound file named 'Cue exposure voiceover' from the laptop. After the task, the patient completes the last page of the questionnaire, Time 2 post cue exposure task question.
7. Patient fills in ARTS patient satisfaction questionnaire.
8. Upload data from the electronic diary. The patient has now finished using the phone and it must be returned at this stage. Check **overall compliance** (refer to electronic diary guidance Appendix xx). If patient has 60% compliance or above, pay £75. If patient has less than 60% compliance pay £40. The patient must sign for receipt of payment. Use the payment form. Sign the phone back in. Return the phone to trial coordinator.
9. Book next appointment using ARTS online system. The next appointment is due in four weeks.
10. Log on to the ARTS online system and enter CRF data  
<https://www.pc-crtu.bham.ac.uk/ARTS/>



**Session 9**

+12 weeks post quit day

**Summary of session 9**

1	Complete first part of the CRF(Pg 20)
2	Patient fills ARTS study questionnaire, week +12 (in folder)
3	Visual probe task
4	CO measurement
5	Pictorial Stroop task
6	Cue exposure task
7	Pay patient £15
8	Book next appointment
9	Data entry of Week +12 CRF on ARTS online system

1. Complete the first part of the CRF (page 20).
2. Give the patient the ARTS week +12 questionnaire to fill, up to where the first break is indicated.
3. Set up visual probe task. There is a break after 8 minutes should the patient need one. This is expected to last for approximately 16 minutes.
4. CO measurement.
5. Set up pictorial Stroop task on laptop. There are three breaks during the task should the patient need them. This task is expected to take approximately 12 minutes in total.
6. Patient to refer back to questionnaire and fill in Time 1, pre cue exposure task question. Set up cue exposure task (cigarette, lighter and a box), play the sound file named 'Cue exposure voiceover' from the laptop. After the task, the patient completes the last page of the questionnaire, Time 2 post cue exposure task question.

7. Pay patient £15, let patient sign on receipt for the money.
8. Book next appointment for 12 weeks time, and print out to patient. Agree with patient way of reminding them of the appointment nearer the date.
9. Log on to the ARTS online system and enter CRF data  
<https://www.pc-crtu.bham.ac.uk/ARTS/>

**Session 10**

+24 weeks post quit day

**Summary of session 10**

1	Complete first part of CRF (Pg 22)
2	Patient fills ARTS study questionnaire, week +24 (in folder)
3	Visual probe task
4	CO measurement
5	Pictorial Stroop task
6	Cue exposure task
7	Final visit – pay patient £15 and thank patient
8	Data entry of Week +24 CRF on ARTS online system

1. Complete the first part of the CRF (Page 22)
2. Give the patient the ARTS week +24 questionnaire to fill, up to where the first break is indicated.
3. Set up visual probe task. There is a break after 8 minutes should the patient need one. This is expected to last for approximately 16 minutes.
4. CO measurement
5. Set up pictorial Stroop task on laptop. There are three breaks during the task should the patient need them. This task is expected to take approximately 12 minutes in total.
6. Patient to refer back to questionnaire and fill in Time 1, pre cue exposure task question. Set up cue exposure task (cigarette, lighter and a box), play the sound file named 'Cue exposure voiceover' from the laptop. After the task, the patient completes the last page of the questionnaire, Time 2 post cue exposure task question.

7. Pay patient £15, let patient sign on receipt for the money. This is the final session. Thank patient for taking part in the study.
8. Log on to the ARTS online system and enter CRF data  
<https://www.pc-crtu.bham.ac.uk/ARTS/>

# APPENDICES

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Appendix 1: Visual probe task guide

Appendix 2: Pictorial Stroop task guide

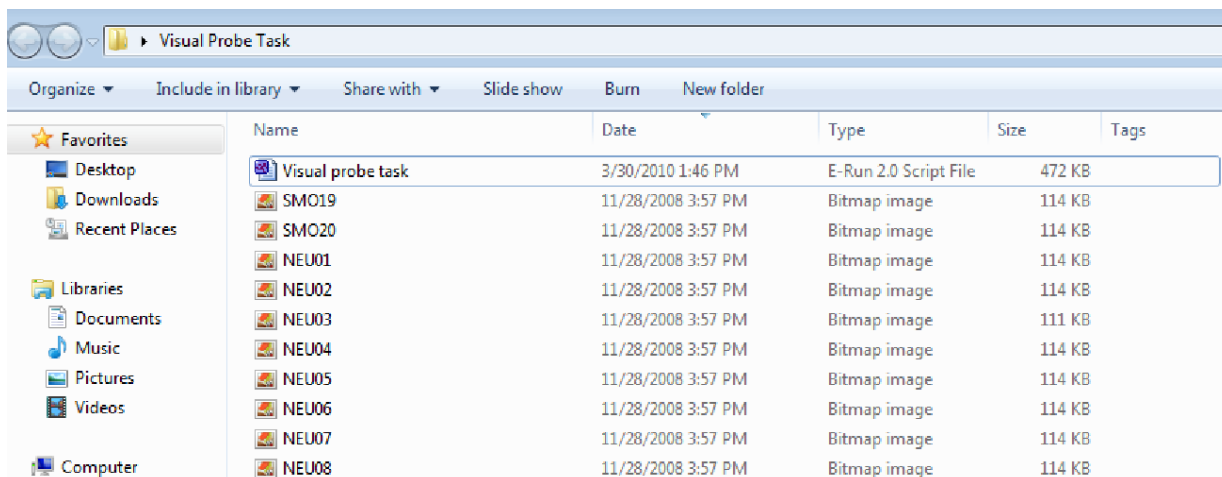
Appendix 3: Cue exposure task guide

Appendix 4: Training guide

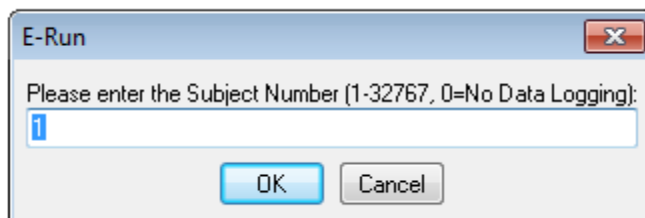
## Appendix 1: Visual Probe Task

N.B. This only applies for the baseline visit (week -2), +4 week visit, +8 week visit, +12 week and +24 week visit.

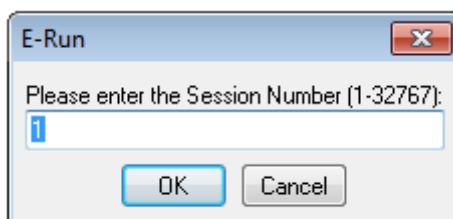
1. Double-click on the Visual Probe Task folder on the desktop. Double-click on the file name 'Visual probe task' (make sure this is the E-run 2.0 Script File)



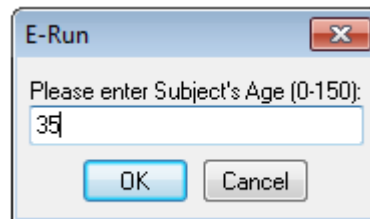
2. After you have clicked on the 'Visual probe task' icon, the following box will appear on the screen. Please type in the patient ID as the subject number, e.g if the patient ID is 0005, type in the number '5' in the box.



3. Type in the Session number, e.g. if this is the baseline visit (week -2 visit), type the number '1', or if this is the week -1 visit, type the number '2', or for week 0 quit day visit, type '3' and so on.

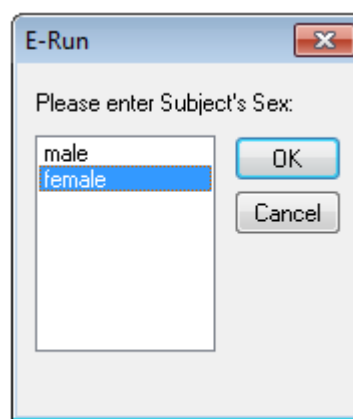


4. Type in the patient's age.




A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Age (0-150):". Below this text is a text input field containing the number "35". At the bottom of the dialog are two buttons: "OK" and "Cancel".

5. Specify whether the patient is male or female by clicking on one of the options.



A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Sex:". Below this text is a list box containing two options: "male" and "female". The "female" option is currently selected and highlighted in blue. To the right of the list box are two buttons: "OK" and "Cancel".

6. Check the information you have entered. If the information is correct, click 'Yes' and proceed on to the instructions page. If any of the information is incorrect, click 'No', which will take you back to the beginning.



A dialog box titled "Summary of Startup Info" with a close button (X) in the top right corner. On the left side, there is a blue circular icon with a white question mark. To the right of the icon, the following information is displayed: "Subject: 1", "Session: 1", "Age: 35", and "Sex: female". Below this information is the text "Continue with the above startup info?". At the bottom of the dialog are three buttons: "Yes", "No", and "Cancel".

7. The instructions screen looks like this. When the patient is ready to proceed they should press any key to start.

### Instructions

You will see two pictures appear on the screen. You should try and ignore these pictures and keep your eyes in the centre of the screen. When the pictures have disappeared you will see a shape appear.

YOUR TASK is to decide if the shape is a circle or a square.

Press the UP ARROW if it is a Circle  
Press the DOWN ARROW if it is a Square

8. The patient will see this screen at the end of the session.

The session is now over.

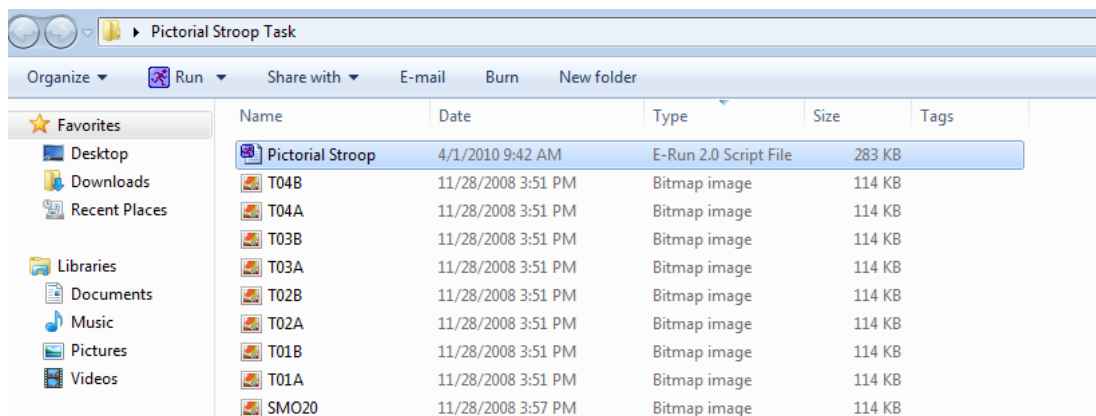
Thank you for taking part.



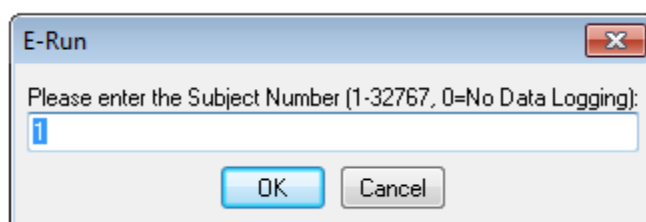
## Appendix 2: Pictorial Stroop Task

N.B. This only applies for the baseline visit (week -2), +4 week visit, +8 week visit, +12 week and +24 week visit.

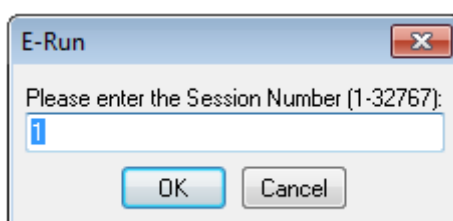
1. Double-click on the Pictorial Stroop Task folder on the desktop. Double-click on the file name 'Pictorial Stroop task' (make sure this is the E-run 2.0 Script File)



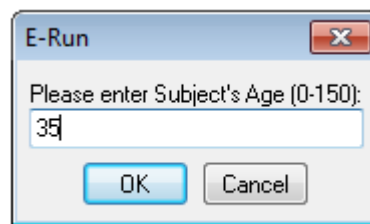
2. After you have clicked on the 'Pictorial Stroop task' icon, the following box will appear on the screen. Please type in the patient ID as the subject number, e.g if the patient ID is 0005, type in the number '5' in the box.



3. Type in the Session number, e.g. if this is the baseline visit (week -2 visit), type the number '1', or if this is the week -1 visit, type the number '2', or for week 0 quit day visit, type '3' and so on.

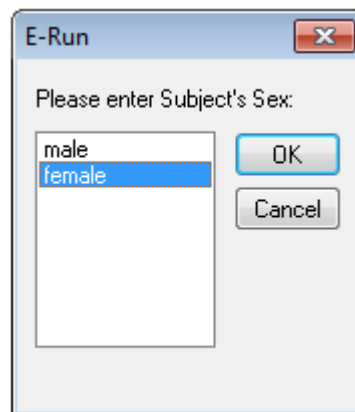


4. Type in the patient's age.



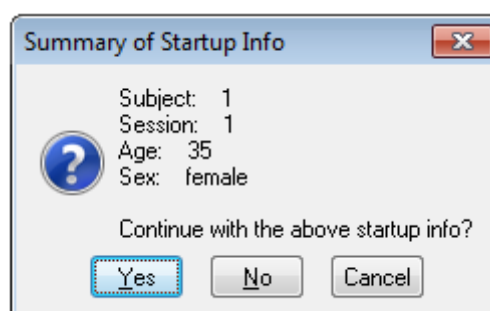
A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Age (0-150):". Below this text is a text input field containing the number "35". At the bottom of the dialog are two buttons: "OK" and "Cancel".

5. Specify whether the patient is male or female by clicking on one of the options.



A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Sex:". Below this text is a list box containing two options: "male" and "female". The "female" option is currently selected and highlighted in blue. To the right of the list box are two buttons: "OK" and "Cancel".

6. Check the information you have entered. If the information is correct, click 'Yes' and proceed on to the instructions page. If any of the information is incorrect, click 'No', which will take you back to the beginning.



A dialog box titled "Summary of Startup Info" with a close button (X) in the top right corner. On the left side, there is a blue circular icon with a white question mark. To the right of the icon, the following information is displayed: "Subject: 1", "Session: 1", "Age: 35", and "Sex: female". Below this information, the text "Continue with the above startup info?" is shown. At the bottom of the dialog are three buttons: "Yes", "No", and "Cancel".

The instructions screen looks like this. When the patient is ready to proceed they should press any key to start.

Instructions

Please respond to each picture presented:

Red button if the picture is in red  
Blue button if the picture is in blue  
Yellow button if the picture is in yellow  
Green button if the picture is in green

Try to respond as quickly and accurately as possible.

When you are ready to begin please press any key to try some practice trials.

7. There is a break in the middle of the task should the patient need a break. Please instruct the patient to proceed by pressing any key to continue.

Get ready for the next Block.

Press any key when you are ready to begin.

8. The patient will see this screen at the end of the session.

The session is now over.

Thank you for taking part.

**Appendix 3: Cue exposure task**

N.B. This only applies for week –1 visit, +4 week visit, +8 week visit, +12 week and +24 week visit.

1. In the equipment given to you, you will have a cigarette, a lighter and a box. Place the cigarette and lighter under the box, without the patient seeing you do this. Place the box in front of the patient
2. Ask the patient to fill in ‘Time 1’ of the patient questionnaire. Time 1 looks like this:

**Time 1**

**Using a vertical line, please mark on the scale how much you are feeling the urge to smoke right now.**

Urge to smoke

Extremely

Not at all

I—————I

**BREAK**

**Please do not turn over until you are instructed to do so**

3. At the break, play the sound file named ‘Cue exposure voiceover’. These are 3 minute instructions. The patient will hear the following instructions.

N.B. At no point will the patient be allowed to light or smoke the cigarette.

00:00

***Do not touch anything until instructed to do so. Please sit quietly and relax for one minute.***

01:00

***Please lift-up the box in front of you and place it to the side.***

*(Patient obeys)*

01:15

***Pick-up the cigarette and hold the cigarette in which ever hand is comfortable.***

*(Patient holds the cigarette)*

01:30

***Pick-up the lighter with your other hand. Hold the cigarette in front of you and hold the lighter.***

*(Patient picks up the lighter)*

01:45

***Hold the cigarette at a downward angle in front of you while continuing to hold the lighter in your other hand.***

*(Patient obeys)*

02:15

***Put the lighter down on the table. Hold the cigarette in your hand as you usually would.***

*(Patient obeys)*

02:30

***Look at the cigarette. Imagine what it would be like to be smoking the cigarette.***

*(Patient obeys)*

02:45

***Please put the cigarette down. Cover the cigarette and the lighter with the box.***

*(Patient does so)*

03 :00

*(Exposure ends)*

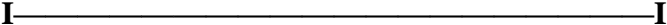
4. Ask the patient to fill in 'Time 2' of the patient questionnaire. Time 2 looks like this:

## **Time 2**

Using a vertical line, please mark on the scale how much you are feeling the urge to smoke right now.

Urge to smoke

Extremely	Not at all
I	I

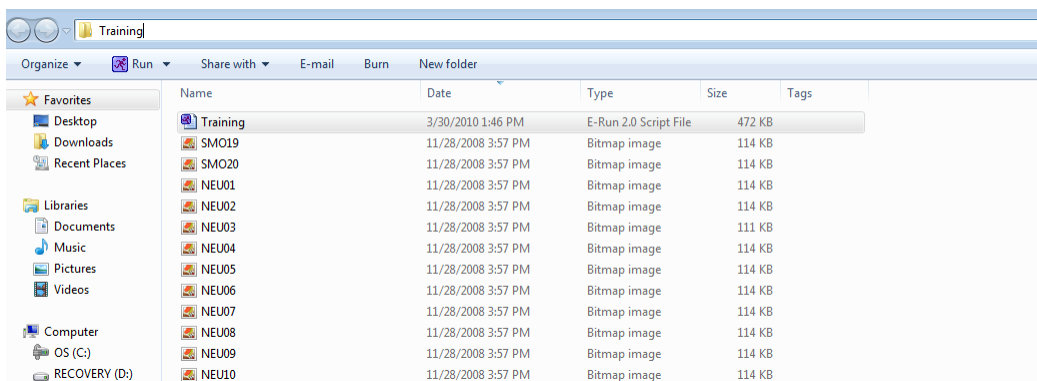


**Thank you very much for completing this questionnaire**

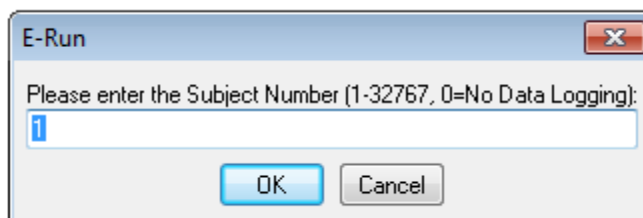
## Appendix 4: Training

N.B. This only applies to week -1 visit, week 0 quit day visit, +1 visit, +2 visit, +3 visit and + 4 visit.

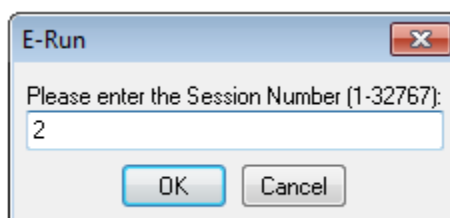
1. Double-click on the Training folder on the desktop. Double-click on the file name 'Training' (make sure this is the E-run 2.0 Script File)



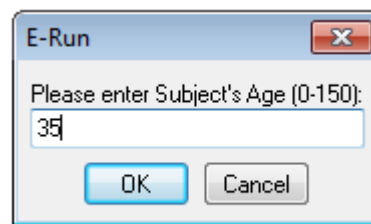
2. After you have clicked on the 'Training' icon, the following box will appear on the screen. Please type in the patient ID as the subject number, e.g if the patient ID is 0005, type in the number '5' in the box.



3. Type in the Session number, e.g. if this is the week -1 visit, type the number '2', or for week 0 quit day visit, type '3' and so on.

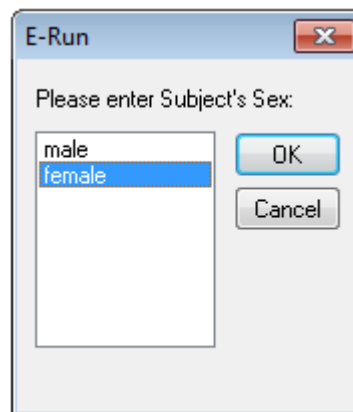


4. Type in the patient's age.




A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Age (0-150):". Below this text is a text input field containing the number "35". At the bottom of the dialog are two buttons: "OK" and "Cancel".

5. Specify whether the patient is male or female by clicking on one of the options.



A dialog box titled "E-Run" with a close button (X) in the top right corner. The text inside says "Please enter Subject's Sex:". Below this text is a list box containing two options: "male" and "female". The "female" option is currently selected and highlighted in blue. To the right of the list box are two buttons: "OK" and "Cancel".

6. Check the information you have entered. If the information is correct, click 'Yes' and proceed on to the instructions page. If any of the information is incorrect, click 'No', which will take you back to the beginning.



A dialog box titled "Summary of Startup Info" with a close button (X) in the top right corner. On the left side, there is a blue circular icon with a white question mark. To the right of the icon, the following information is displayed: "Subject: 1", "Session: 2", "Age: 35", and "Sex: female". Below this information, the text "Continue with the above startup info?" is shown. At the bottom of the dialog are three buttons: "Yes", "No", and "Cancel". The "Yes" button is highlighted with a dashed border.

7. The instructions screen looks like this. When the patient is ready to proceed they should press any key to start.



Instructions

You will see two pictures appear on the screen. You should try and ignore these pictures and keep your eyes in the centre of the screen. When the pictures have disappeared you will see a shape appear.

YOUR TASK is to decide if the shape is a circle or a square.

Press the UP ARROW if it is a Circle  
Press the DOWN ARROW if it is a Square

8. At the end of the first block, the patient will come to a screen which looks like this.

End of Part 1

Take a break

9. After the patient has had a break and is ready to resume with the second part of the task, ask the patient to press any key to continue. A screen like this will appear.

Ready for Part 2?

Remember

Press the UP ARROW if the shape is a CIRCLE  
Press the DOWN ARROW if the shape is a SQUARE

Press any key to continue

10. The patient will see this screen at the end of the session.

The session is now over.

Thank you for taking part.

## Appendix 16. Case report form for ARTS trial

<b>ARTS</b>														
UNIVERSITY OF BIRMINGHAM		<b>Case Report Form</b>												
Participant ID Number:		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>								
Participant Date of Birth		<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>				
<b>RANDOMISATION GROUP</b> (write in space 'A' or 'B')														
Session	Date <i>dd / mm / yyyy</i>	Attended		Questionnaires Completed?		Electronic Diary Completed?								
		Yes	No	Yes	No	Yes	No							
(1) -2 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									
(2) -1 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(3) 0 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(4) +1 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(5) +2 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(6) +3 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(7) +4 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(8) +8 wk	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							
(9) 3m post quit	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									
(10) 6m post quit	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									
<b>Summary Sheet</b>														
Please insert Participant's ID number on each page								<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	1

Event	Date Commenced dd / mm / yyyy	Date Stopped dd / mm / yyyy	Yes = 1 No = 2		Nurse initials
Quit smoking at week +4 (NHS) (see below)	__ / __ / ____	N/A	Validated	Self-report	
Quit smoking at week +4 (RS) (see below)	__ / __ / ____	N/A	Validated	Self-report	
Abandoned this quit attempt	N/A	__ / __ / ____			
Quit smoking at week +8 (RS) (see below)	__ / __ / ____	N/A	Validated	Self-report	
Withdrawn from study	N/A	__ / __ / ____			
Moderate/Severe Adverse Event(s) ( <i>graded 3 or above for "caused by study medication" on adverse events form</i> )	__ / __ / ____	__ / __ / ____			
Serious Adverse Event(s)	__ / __ / ____	__ / __ / ____			
Quit smoking at 3 months (RS) (see below)	__ / __ / ____	N/A	Validated	Self-report	
Quit smoking at 6 months (RS) (see below)	__ / __ / ____	N/A	Validated	Self-report	
Made a new quit attempt	__ / __ / ____	N/A			
Lost to follow-up at +8	N/A	__ / __ / ____			
Lost to follow-up at 3 months	N/A	__ / __ / ____			
Lost to follow-up at 6 months	N/A	__ / __ / ____			

### Definitions of quit

Time of quit	Definition
+ 4 week (NHS)	No cigarettes at all (not even 1 puff) since week +2 verified by CO of <10
+ 4 week (RS)	No more than 5 cigarettes since week +2 verified by CO of <10
+ 8 week (RS)	No more than 5 cigarettes since week +2 verified by CO of <10
3 month (RS)	No more than 5 cigarettes since week +2 verified by CO of <10
6 month (RS)	No more than 5 cigarettes since week +2 verified by CO of <10

**NB: since week +2 means at the end of the second week post quit date – verify by using data collected at weeks +3 onwards visits and NOT DATA FROM THE WEEK +2 VISIT**

### Assessment form to decide eligibility for ARTS study

Please insert Participant's ID number on each page

2

**ARTS checklist inclusion criteria****Section 1** Please complete for *all* subjects

Is the participant:			
18 years of age or older	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Willing to attempt to quit smoking completely in two weeks	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Willing and able to comply with all study procedures	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Does the participant:			
Smoke at least 10 cigarettes a day <u>OR</u> blows greater than or equal to 10 on CO monitor	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Have normal or corrected-to-normal vision	Yes	<input type="checkbox"/>	No <input type="checkbox"/>

If **NO** is the answer to **any** of the above questions in **section 1** the participant is unable to participate in this study.

**ARTS checklist exclusion criteria****Section 2** Please complete for *all* subjects

Does the participant have:

A medical condition that prevents them seeing the computerised images properly, attending to the task, or pressing the keyboard buttons on the computer accurately, or completing any other study procedures	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Severe adverse reactions to nicotine patches?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Severe extensive dermatitis/eczema?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Severe renal impairment (i.e. GFR $\leq$ 29mls/min)?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
Severe hepatic impairment?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
A severe acute or chronic psychiatric or medical condition that inhibits their ability to complete the trial?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>

Is the person using any of the following medications?

NRT, bupropion, nortriptyline, mecamylamine, reserpine, varenicline?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
--	-----	--------------------------	-----------------------------

Has the participant:

Taken part in any other medicinal trials within the last 3 months?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
--	-----	--------------------------	-----------------------------

Please insert Participant's ID number on each page

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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3

**Definitions**

<b>Severe adverse reaction to NRT</b>	a) any reaction that has made them feel very unwell to the extent they wouldn't be prepared to use it again, or/and b) patches only – sore, open and blistering skin, or/and localised swelling of tissues
<b>Severe extensive dermatitis/eczema</b>	Insufficient areas of skin available to place the patch on intact skin or skin so reactive that likely to react to patch based on past use of patches/elastoplast or similar.
<b>Severe hepatic impairment</b>	Liver damage to the extent that GP has to reduce their normal medications due to toxicity.
<b>Severe acute or chronic psychiatric or medical condition</b>	Any unstable or terminal existing condition that may either make it unsafe for one to one appointments for the member of staff or put the participant in a compromising position.

If YES is the answer to any of the above questions in section 2 the participant is unable to participate in this study.

If you are unsure on any of the inclusion / exclusion criteria you must discuss with the trial doctor or trial manager whether the person can participate in this study.

Name of person spoken to (if applicable) .....

Have you completed medical history (pg 5)? Yes ☐ No ☐

Have you completed concomitant medication (pg 6)? Yes ☐ No ☐

Is the person able to enter the trial? Yes ☐ No ☐

**Trial Office**

Copy of consent to GP Yes ☐ No ☐ Date sent \_\_\_\_/\_\_\_\_/\_\_\_\_

Copy of consent to patient Yes ☐ No ☐ Date given \_\_\_\_/\_\_\_\_/\_\_\_\_

GP letter sent informing of trial entry Yes ☐ No ☐ Date sent \_\_\_\_/\_\_\_\_/\_\_\_\_

Response from GP Yes ☐ No ☐ Date received \_\_\_\_/\_\_\_\_/\_\_\_\_

GP withdrawn from trial Yes ☐ No ☐

**Summary note**

\_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
Name of assessor Date of assessment Signature

Please insert Participant's ID number on each page

4

Medical History Form	
No.	Current medical conditions
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Please insert Participant's ID number on each page

5

## Concomitant Medication Form

Has the participant:

Used any form of antidepressant medication in the past but is not taking any at present?      Yes ☐      No ☐

No	Current medications
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Initials \_\_\_\_

Please insert Participant's ID number on each page

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Visit 2: Randomisation week	-1 week pre-quit
Advisor Name	<input style="width: 100%;" type="text"/>
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>
Time of visit	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Confirm consent	Yes <input type="checkbox"/> No <input type="checkbox"/>
Confirm eligibility	Yes <input type="checkbox"/> No <input type="checkbox"/>
C0 measurement	<input style="width: 100%;" type="text"/>
Has participant brought diary to appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Diary completed?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Diary checked/downloaded?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed -1 wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed -1wk pre cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Cue exposure task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed -1wk post cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
RANDOMISATION carried out on ARTS website?	Yes <input type="checkbox"/> No <input type="checkbox"/>
<b>N.B. Make note of group on page 1 of CRF</b>	
Training part 1 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Behavioural support given?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Patches issued?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Training part 2 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant made appointment for next week, card filled in?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Length of today's appointment _____ mins	
Comments: _____	
Date: ____/____/____	Initials: ____
Please insert Participant's ID number on each page <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	

Visit 3: Quit day		0wk
Advisor Name	<input style="width: 100%;" type="text"/>	
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Time of visit	<input style="width: 40px;" type="text"/> <input style="width: 40px;" type="text"/> <input style="width: 40px;" type="text"/> <input style="width: 40px;" type="text"/>	
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant smoked their last cigarette?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Date of last cigarette	___ / ___ / ____	
C0 measurement	<input style="width: 100%;" type="text"/>	
Any new medications checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Any new medical history checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed 0 wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant brought diary to appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary completed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary checked/downloaded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Training part 1 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Behavioural support given?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Patches for next week issued?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Training part 2 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant made appointment for next week, card filled in?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Length of today's appointment _____ mins		
Comments: _____ _____		
Date: ___ / ___ / ____      Initials: ____		
Please insert Participant's ID number on each page <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> 9		



Length of today's appointment \_\_\_\_\_ mins

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date:        \_\_ \_\_ / \_\_ \_\_ / \_\_ \_\_ \_\_ \_\_

Initials:   \_\_ \_\_    \_\_ \_\_

Please insert Participant's ID number on each page

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<b>Visit 5: 2 weeks post-quit day</b>	<b>+2wk</b>
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Advisor Name

Date    **2** **0**

Time of visit

Did participant attend appointment? Yes ☐ No ☐

Has participant smoked since last visit? Yes ☐ No ☐

If yes, how many cigarettes?

Has participant abandoned quit attempt? Yes ☐ No ☐

If yes, date returned to smoking:  /  /

C0 measurement

Any new medications checked and recorded? Yes ☐ No ☐

Any new medical history checked and recorded? Yes ☐ No ☐

Has participant completed +2wk pre task questions? Yes ☐ No ☐

Has participant brought diary to appointment? Yes ☐ No ☐

Diary completed? Yes ☐ No ☐

Diary checked/downloaded? Yes ☐ No ☐

Training part 1 computer task performed? Yes ☐ No ☐

Behavioural support given? Yes ☐ No ☐

Is participant wearing patch? Yes ☐ No ☐

If no, date stopped wearing patch  /  /

Any side effects/adverse events? Yes ☐ No ☐

Patches for next week issued? Yes ☐ No ☐

Training part 2 computer task performed? Yes ☐ No ☐

Has participant made appointment for next week, card filled in? Yes ☐ No ☐

Please insert Participant's ID number on each page

12

Length of today's appointment \_\_\_\_\_ mins

Comments:

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Date:        \_\_\_ / \_\_\_ / \_\_\_\_\_

Initials:    \_\_\_    \_\_\_

Please insert Participant's ID number on each page

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353

Length of today's appointment \_\_\_\_\_ mins

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date:        \_\_ \_\_ / \_\_ \_\_ / \_\_ \_\_ \_\_ \_\_

Initials:   \_\_ \_\_   \_\_ \_\_

Please insert Participant's ID number on each page

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Visit 7: 4 weeks post-quit day		+4wk
Advisor Name	<input style="width: 100%;" type="text"/>	
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Time of visit	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant smoked since last visit?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, how many cigarettes? <input style="width: 100px;" type="text"/>		
Has participant abandoned quit attempt?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, date returned to smoking: <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/>		
CO measurement	<input style="width: 100%;" type="text"/>	
Any new medications checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Any new medical history checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed +4wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant brought diary to appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary completed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary checked/downloaded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has the participant completed the visual probe computer task? <b>N.B. There is one break in the task</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Behavioural support given?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
<b>N.B. Participants are not seen again for 4 weeks</b>		
Is participant wearing patch?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If no, date stopped wearing patch <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/>		
Any side effects/adverse events?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
3 weeks of NRT issued?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
OR 3 week prescription issued?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Please insert Participant's ID number on each page <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>		

Has participant completed pictorial Stroop task? **N.B There are 3 breaks in the task** Yes ☐ No ☐

Has participant completed +4wk pre cue exposure task questions? Yes ☐ No ☐

Cue exposure task performed? Yes ☐ No ☐

Has participant completed +4wk post cue exposure task questions? Yes ☐ No ☐

Has participant been told to use their diary for a further 1 week? Yes ☐ No ☐

Has participant made appointment for next week, card filled in? **N.B. Participants are not seen again for 4 weeks** Yes ☐ No ☐

Length of today's appointment \_\_\_\_\_mins

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Initials: \_\_\_\_

Please insert Participant's ID number on each page

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**Visit 8: 8 weeks post-quit day****+8wk**

Advisor Name

Date

  2 0 

Time of visit

Did participant attend appointment?

Yes ☐ No ☐

Has participant smoked since last visit?

Yes ☐ No ☐

If yes, how many cigarettes?

Has participant abandoned quit attempt?

Yes ☐ No ☐

If yes, date returned to smoking:

 /  / 

CO measurement

Any new medications checked and recorded?

Yes ☐ No ☐

Any new medical history checked and recorded?

Yes ☐ No ☐

Has participant completed +8wk pre task questions?

Yes ☐ No ☐Has the participant completed the visual probe computer task? **N.B. There is one break in the task**Yes ☐ No ☐Has participant completed pictorial Stroop task? **N.B There are 3 breaks in the task**Yes ☐ No ☐

Has participant completed +8wk pre cue exposure task questions?

Yes ☐ No ☐

Cue exposure task performed?

Yes ☐ No ☐

Has participant completed +8wk post cue exposure task questions?

Yes ☐ No ☐

Has participant completed patient satisfaction questionnaire?

Yes ☐ No ☐

Has participant brought diary to appointment?

Yes ☐ No ☐

Diary checked/downloaded?

Yes ☐ No ☐

Has the diary been returned?

Yes ☐ No ☐

Has participant received payment?

Yes ☐ No ☐

Please insert Participant's ID number on each page

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**N.B. Participants are not seen again for another 4 weeks**Is participant wearing patch? Yes ☐ No ☐

If no, date stopped wearing patch \_\_\_\_/\_\_\_\_/\_\_\_\_

Any side effects/adverse events? Yes ☐ No ☐4 weeks of NRT issued? Yes ☐ No ☐OR 4 week prescription issued? Yes ☐ No ☐Has appointment been made in 4 weeks' time? Card filled in? Yes ☐ No ☐

Length of today's appointment \_\_\_\_\_ mins

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Initials: \_\_\_\_

Please insert Participant's ID number on each page ☐☐☐☐☐☐

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Visit 9: 12 weeks post-quit day		+12wk
Advisor Name	<input style="width: 100%;" type="text"/>	
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Time of visit	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant smoked since last visit?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, how many cigarettes? _____		
Has participant abandoned quit attempt?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, date returned to smoking: ____ / ____ / ____		
C0 measurement	<input style="width: 100%;" type="text"/>	
Any new medications checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Any new medical history checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed +12wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has the participant completed the visual probe computer task? <b>N.B. There is one break in the task</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed pictorial Stroop task? <b>N.B There are 3 breaks in the task</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed +12wk pre cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Cue exposure task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed +12wk post cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Is participant wearing patch?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If no, date stopped wearing patch ____ / ____ / ____		
Any side effects/adverse events?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant received £15 payment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
<b>N.B. Participants are not seen again for another 3 months</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has appointment been made in 3 months' time? Card filled in?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Please insert Participant's ID number on each page <input style="width: 60px;" type="text"/> 20		

Length of today's appointment \_\_\_\_\_ mins

Comments: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Date:        \_\_ \_\_ / \_\_ \_\_ / \_\_ \_\_ \_\_ \_\_

Initials:   \_\_ \_\_    \_\_ \_\_

Please insert Participant's ID number on each page

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<b>Visit 10: 24 weeks post-quit day</b>	<b>+24wk</b>
Advisor Name	<input style="width: 100%;" type="text"/>
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>
Time of visit	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant smoked since last visit?	Yes <input type="checkbox"/> No <input type="checkbox"/>
If yes, how many cigarettes? <input style="width: 100%;" type="text"/>	
Has participant abandoned quit attempt?	Yes <input type="checkbox"/> No <input type="checkbox"/>
If yes, date returned to smoking: <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/>	
C0 measurement	<input style="width: 100%;" type="text"/>
Any new medications checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Any new medical history checked and recorded?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed +24 wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has the participant completed the visual probe computer task? <b>N.B. There is one break in the task</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed pictorial Stroop task? <b>N.B There are 3 breaks in the task</b>	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed + 24 wk pre cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Cue exposure task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant completed +24 wk post cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Has participant received £15 payment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Length of today's appointment <input style="width: 100px;" type="text"/> mins	
Comments: <input style="width: 100%;" type="text"/>	
<input style="width: 100%;" type="text"/>	
<input style="width: 100%;" type="text"/>	
<input style="width: 100%;" type="text"/>	
Date: <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/> - <input style="width: 20px;" type="text"/>	Initials: <input style="width: 40px;" type="text"/>
Please insert Participant's ID number on each page <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> 22	

Appendix: EXTRA Visit (Did not attend visit 2) Randomisation week		-1 week pre-quit
Advisor Name	<input style="width: 100%;" type="text"/>	
Date	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Time of visit	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
Did participant attend appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Confirm consent	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Confirm eligibility	Yes <input type="checkbox"/> No <input type="checkbox"/>	
C0 measurement	<input style="width: 100%;" type="text"/>	
<b>Write new quit date</b>	____ / ____ / ____	
Has participant brought diary to appointment?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary completed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diary checked/downloaded?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed -1 wk pre task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed -1wk pre cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Cue exposure task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant completed -1wk post cue exposure task questions?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
RANDOMISATION carried out on ARTS website?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
<b>N.B. Make note of group on page 1 of CRF</b>		
Training part 1 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Behavioural support given?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Patches issued?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Training part 2 computer task performed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has participant made appointment for next week, card filled in?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Length of today's appointment _____ mins		
Comments:	_____ _____ _____	
Date: ____ / ____ / ____	Initials: ____	
Please insert Participant's ID number on each page	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/>	
	23	



## Adverse Event Form

	Diagnosis/Syndrome /Symptom	Start Date (dd/mm/yy)	Stop Date (dd/mm/yy)	Intensity 1=Mild 2=Moderate 3=Severe	Serious 1=Yes 2=No	Caused by Study? 1=No 2= Unlikely 3=Possibly 4=Probably 5=Yes	Action taken with study? 1=None 2=Intervention changed /how? 3=Intervention discontinued	Outcome at last session 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Death 5=Unknown	Practitioner name and signature
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									

### Withdrawal Report Form

<b>1.</b>	<b>I am reporting that since trial entry:</b>	<b>Yes</b>	<b>No</b>
<b>1a.</b>	Patient has withdrawn completely		

<b>1b.</b>	Date patient withdrew	-----/-----/-----
------------	-----------------------	-------------------

If yes to question 1a, please circle option below or give reason:

Ineligible / Moved away / Withdrawn consent / Quitting by other means / Abandoned quit attempt / Study tasks are an inconvenience / did not state reason / Other (give reason):

<b>2a.</b>	Patient happy to continue to be followed up	<b>Yes</b>	<b>No</b>
------------	---	------------	-----------

If yes to question 2a, go to question 2b

**2b. By which means would the patient like to continue:**  
Please circle preference below:

1. Telephone
2. Clinic visit
3. Home visit

2c	Patient stopped treatment	Yes	No
2d	Date patient stopped	____/____/____	

If yes please give reason below:

Quitting by other means / Abandoned quit attempt / Study tasks are an inconvenience / did not state reason / Other (give reason):

**Appendix 17. Baseline questionnaire**

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

## **ARTS Study Baseline Questionnaire (Week -2)**

**Date:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**Patient ID:**

--	--	--	--	--

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

**Thank you for agreeing to take part in this research.**

Please try to answer all the questions in this questionnaire and ask an advisor if you are unsure of any questions.

Some questions ask you to shade in the circle by the statement that applies to you. Please shade in one circle only for each question apart from where specified.

*Example:*

*If apples are your favourite fruit you would answer the following question like this:*

*Question: What is your favourite fruit?*

Apple	<input checked="" type="radio"/>
Banana	<input type="radio"/>
Orange	<input type="radio"/>

Other questions will ask you to write your answer on a line or in a box. Remember there are no right or wrong answers and all the information you give is confidential.

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

## ABOUT YOU

These questions are about you and your household. They give a picture of who took part in our research.

### 1. How would you describe your ethnic group?

White <input type="radio"/>	Mixed <input type="radio"/>	Indian <input type="radio"/>
Pakistani <input type="radio"/>	Bangladeshi <input type="radio"/>	Asian-other <input type="radio"/>
Black-Caribbean <input type="radio"/>	Black-African <input type="radio"/>	Black-other <input type="radio"/>
Chinese <input type="radio"/>	Chinese-Other <input type="radio"/>	Other ethnic group <input type="radio"/>

### 2. What is your highest educational qualification?

Degree, or equivalent, and above <input type="radio"/>	'A' levels, vocational Level 3 and above <input type="radio"/>
Other qualifications below 'A' level or below vocational level 3 <input type="radio"/>	Other Qualifications (e.g. foreign) <input type="radio"/>
No formal qualifications <input type="radio"/>	

### 3. Are you:

Employed <input type="radio"/>	Unemployed <input type="radio"/>
Looking after home or family <input type="radio"/>	Student <input type="radio"/>
Retired <input type="radio"/>	Long-term sick or disabled? <input type="radio"/>
Other <input type="radio"/>	

«id»

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

If you have selected 'Employed', please continue to question 4, otherwise please proceed to question 6.

**4. Where is your workplace based?**

Indoors	<input type="radio"/>	Outdoors	<input type="radio"/>
---------	-----------------------	----------	-----------------------

**5. Do you use a designated smoking area to smoke where you work?**

Yes	No
<input type="radio"/>	<input type="radio"/>

**6. Do you live with someone that smokes?**

No	<input type="radio"/>	Yes but they do not smoke in the house or flat	<input type="radio"/>
Yes they smoke in the house or flat	<input type="radio"/>		

**7. Do you smoke inside your house?**

Yes	<input type="radio"/>
No	<input type="radio"/>

**8. How old were you when you became a regular smoker? \_\_\_\_\_ years old**

**9. Have you ever tried to stop smoking?**

Yes	<input type="radio"/>	If yes, please continue to question 10.
No	<input type="radio"/>	If no, please continue to question 11.

«id»

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

10. How long have you gone without smoking any cigarettes? \_\_\_\_\_

11. How soon after you wake up do you smoke your first cigarette?

Within 5 minutes <input type="radio"/>	6-30 minutes <input type="radio"/>
31-60 minutes <input type="radio"/>	After 60 minutes <input type="radio"/>

12. Do you find it difficult to refrain from smoking in places where it is forbidden?

Yes	No
<input type="radio"/>	<input type="radio"/>

13. Which cigarette would you hate most to give up?

The first one in the morning	Any other
<input type="radio"/>	<input type="radio"/>

14. Do you smoke more frequently during the first hours after waking than during the rest of the day?

Yes	No
<input type="radio"/>	<input type="radio"/>

15. Do you smoke if you are so ill that you are in bed most of the day?

Yes	No
<input type="radio"/>	<input type="radio"/>

«id»

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

**16. Do you smoke for pleasure or smoke to cope?**

Smoke for pleasure	Smoke to cope
<input type="radio"/>	<input type="radio"/>

**17. How much of the time have you felt the urge to smoke in the past week?  
(Rated on a scale from 1 being the least to 7 being the most)**

1 Not at all	2	3	4	5	6	7 All the time
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**18. How strong have the urges been?**

1 No urges	2	3	4	5	6	7 Extremely strong urges
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**19. How much do you want to give up smoking for good on this attempt?**

1 Not at all	2	3	4	5	6	7 Extremely
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**20. How confident are you that you will give up smoking for good at this attempt?**

1 Not at all	2	3	4	5	6	7 Extremely
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

«id»



A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

**21. Indicate how well each of the following statements describes you:**

	Not at all true	Somewhat true	Moderately true	Very true	Extremely true
a) My cigarette smoking is fairly regular throughout the day.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b) My smoking is not much affected by other things. I smoke about the same amount whether I'm relaxed or working, happy or sad, alone or with others, etc..	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c) I smoke consistently and regularly throughout the day.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d) I smoke about the same amount on weekends as on weekdays.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e) It's hard to estimate how many cigarettes I smoke per day because the number often changes.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f) My smoking pattern is very irregular throughout the day. It is not unusual for me to smoke many cigarettes in an hour, then not have another one until hours later.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g) The number of cigarettes I smoke per day is often influenced by other factors – how I'm feeling, what I'm doing, etc..	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h) I smoke at different rates in different situations.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

**22. We are interested in knowing about when and where you come across cues or triggers that remind you of smoking or make you feel like smoking. For each possible cue below, please rate how much it typically makes you feel like smoking:**

	1 Not at all	2	3	4	5	6	7 Extremely
a) Seeing a pack of cigarettes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b) Seeing a lit cigarette	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c) Seeing someone I don't know smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d) Seeing someone I do know smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e) Seeing someone I know who is a smoker, even if they're not smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f) Seeing matches or a lighter	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g) Seeing cigarettes in an ashtray	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h) Seeing cigarette butts	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i) Seeing an empty ashtray	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
j) Smelling cigarette smoke	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
k) Seeing an image of a cigarette in a picture or movie	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
l) Seeing a cigarette advertisement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

«id»

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Baseline questionnaire v.2, 21/09/10.

**23. Please write down the three situations in which you are most likely to experience strong urges to smoke:**

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

### FEELINGS

**24. Please show for each of the items below how you have been feeling over the past week.**

	1 Not at all	2	3	4	5	6	7 Extremely
a) Depressed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b) Anxious	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c) Irritable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d) Restless	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e) Hungry	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f) Poor concentration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g) Poor sleep at night	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**Thank you very much  
for completing this questionnaire**

«id»

**Appendix 18. Example of Mood and Physical Symptoms Scale (MPSS) questionnaire**

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Questionnaire week 0/+1/+2/+3 v.1, 15/03/10

## ARTS Study Questionnaire

Week 0 ☐

Week +1 ☐

Week +2 ☐

Week +3 ☐

Date.....

Patient ID:

«id»

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Questionnaire week 0/+1/+2/+3 v.1, 15/03/10

**Thank you for agreeing to take part in this research.**

Please try to answer all the questions in this questionnaire and ask an advisor if you are unsure of any questions.

Some questions ask you to shade in the circle by the statement that applies to you. Please shade in one circle only for each question apart from where specified.

*Example:*

*If apples are your favourite fruit you would answer the following question like this:*

*Question: What is your favourite fruit?*

Apple	<input checked="" type="radio"/>
Banana	<input type="radio"/>
Orange	<input type="radio"/>

Other questions will ask you to write your answer on a line or in a box. Remember there are no right or wrong answers and all the information you give is confidential.

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Questionnaire week 0/+1/+2/+3 v.1, 15/03/10

**1. Please show for each of the items below how you have been feeling over the past week.**

	1 Not at all	2	3	4	5	6	7 Extremely
a) Depressed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b) Anxious	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c) Irritable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d) Restless	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e) Hungry	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f) Poor concentration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g) Poor sleep at night	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**2. How much of the time have you felt the urge to smoke in the past week?**

1 Not at all	2	3	4	5	6	7 All the time
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**3. How strong have the urges been?**

1 No urges	2	3	4	5	6	7 Extremely strong urges
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**Thank you very much  
for completing this questionnaire**

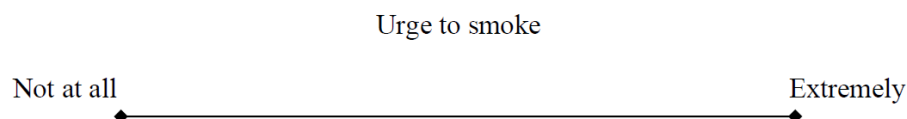
«id»

## **Appendix 19. Example of visual analogue scale (VAS) used to measure urge to smoke pre and post cue exposure task**

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Questionnaire week –1 v1, 15/03/10

### **Time 1- pre task**

**Using a vertical line, please mark on the scale how much you are feeling the urge to smoke right now.**



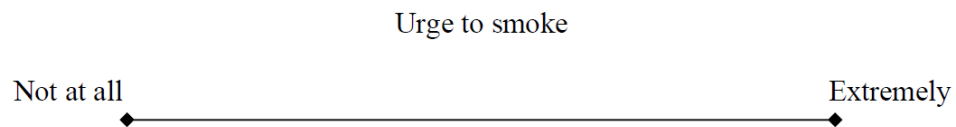
### **BREAK**

**Please do not turn over until you are instructed to do so**

**Cue exposure task – play sound file off laptop**

**Time 2 – post task**

Using a vertical line, please mark on the scale how much you are feeling the urge to smoke right now.



**Thank you very much  
for completing this questionnaire**



**Appendix 20. Question on knowledge of group allocation in +4 week questionnaire**

4. At the start of your treatment, you were randomly allocated to one of two groups: either a group who did computer tasks with training or a group who did computer tasks without training. Which group do you think you were in?

Group with training	<input type="radio"/>
Group without training	<input type="radio"/>
I don't know	<input type="radio"/>

**Thank you very much  
for completing this questionnaire**

**Appendix 21. Patient satisfaction questionnaire**

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient satisfaction questionnaire v.1, 15/03/10

# **ARTS Study Patient Satisfaction Questionnaire**

**Date**.....

**Patient ID:**

--	--	--	--	--

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient satisfaction questionnaire v.1, 15/03/10

**1. How difficult were the instructions to understand?**

Not at all difficult	Slightly difficult	Somewhat difficult	Very difficult	Extremely difficult
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**2. How difficult did you find the task?**

Not at all difficult	Slightly difficult	Somewhat difficult	Very difficult	Extremely difficult
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**3. Was the length of the task convenient for you at each session?**

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**4. How convenient was it for you to carry out the task each week?**

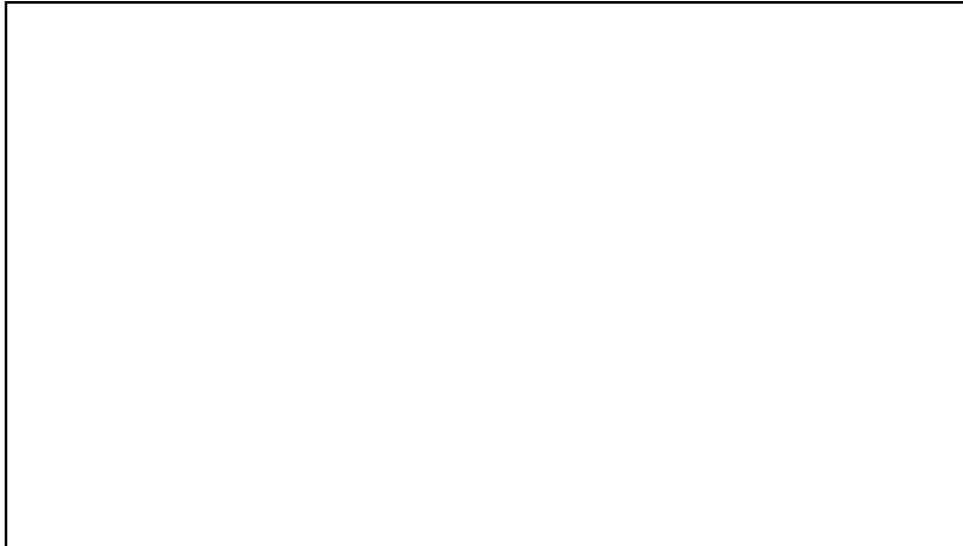
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**5. Would you use this task if it helped you in your attempt to stop smoking?**

No	Yes with lots of reservations	Yes with some reservations	Yes wholeheartedly
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). Patient satisfaction questionnaire v.1, 15/03/10

**If you answered ‘Yes with lots of reservations’ or ‘Yes with some reservations’ what reservations would you have?**



**6. What suggestions do you have or improvements would you like to see made?**



4. At the start of your treatment, you were randomly allocated to one of two groups: either a group who did computer tasks with training or a group who did computer tasks without training. Which group do you think you were in?

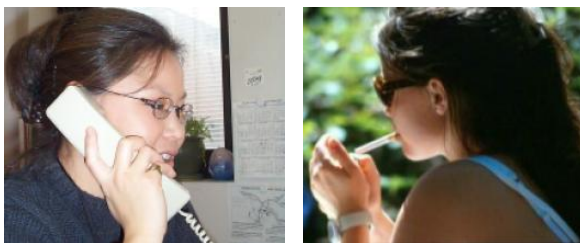
Group with training	<input type="radio"/>
Group without training	<input type="radio"/>
I don't know	<input type="radio"/>

**Thank you very much  
for completing this questionnaire**

---

**Appendix 22. Stimuli used during assessment and training tasks**

Picture-pair 1



Picture-pair 2



Picture-pair 3



Picture-pair 4



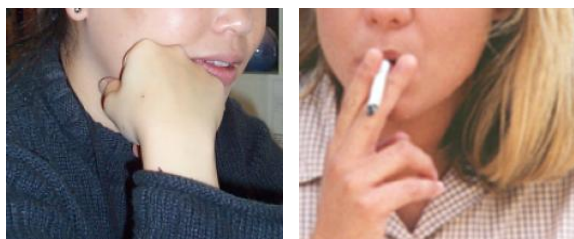
Picture-pair 5



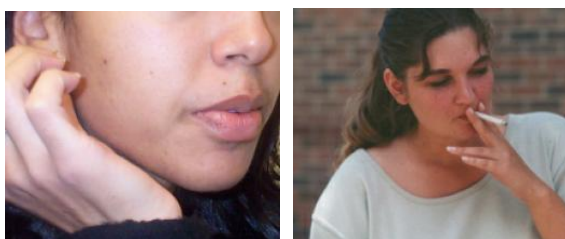
Picture-pair 6



Picture-pair 7



Picture-pair 8



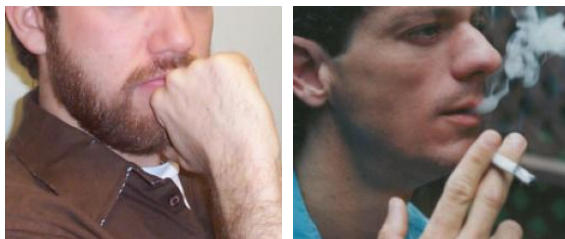
Picture-pair 9



Picture-pair 10



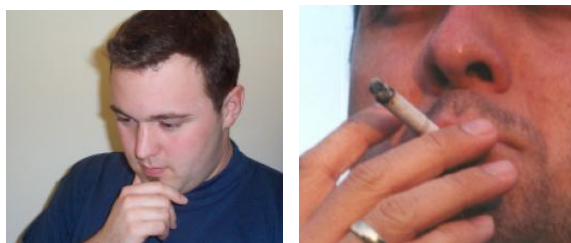
Picture-pair 11



Picture-pair 12



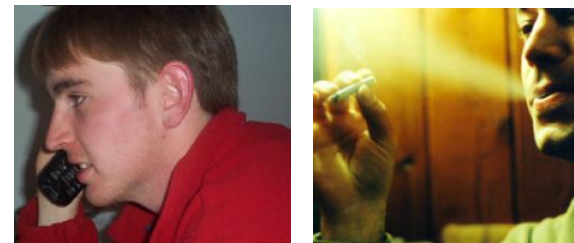
Picture-pair 13



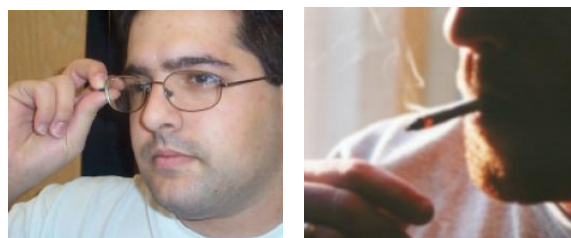
Picture-pair 14



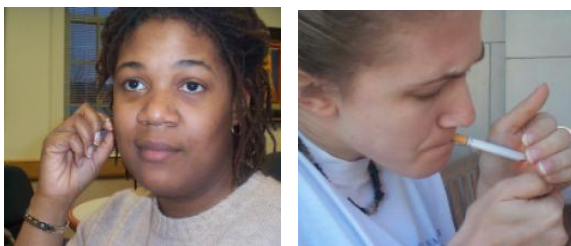
Picture-pair 15



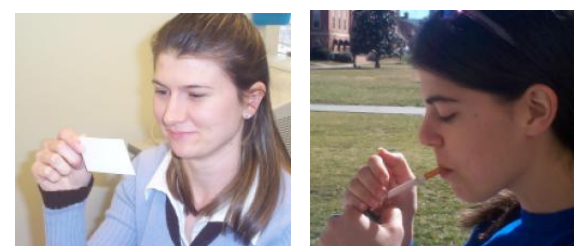
Picture-pair 16



Picture-pair 17



Picture-pair 18





**Appendix 23. Letter of ethics approval for ARTS trial**

## Appendix 24. ARTS posters

**ARTS**

**Do you want to stop smoking but find it hard to overcome those cravings?**

**We are currently running a research study here at the University to see if a new computer-based training package can help smokers quit.**

**Come along to our 7-week stop smoking programme where you will receive standard NHS behavioural support, nicotine patches, and computer-based training.**

**You will be compensated for your time.**

**For more information call us today on:  
0121 414 3027 or text your name to:  
07845877993**

UNIVERSITY OF BIRMINGHAM

NHS

A randomised controlled trial of attentional bias retraining in cigarette smokers attempting smoking cessation (ARTS). University Poster V.1 20/07/2011

## Appendix 25. Facebook campaign

facebook

Last 7 days Sep 19 — Sep 25 All except deleted Select rows to edit Full report 1 result

Name	Campaign	Status	Reach	Freq.	Social reach	Actions	Clicks	CTR	Bid	Price
Quit smoking for research	My Adverts		0	0.0	0	0	0	0.000%	\$1.30	\$0.0

**Advert Preview** Edit

**Quit smoking for research**  
birmingham.ac.uk

**ARTS**

You may be eligible to take part in a stop smoking study at the University of Birmingham and may be compensated up to £75 for your time

[View on site](#) · [Create a similar advert](#)

**Targeting** Edit

This advert targets 806,800 users:

- who live in the United Kingdom
- who live within 16 kilometres of Birmingham
- age 18 and older

Suggested bid: \$0.75–1.73 USD

**Performance**

CTR

1.0 %

0.5 %

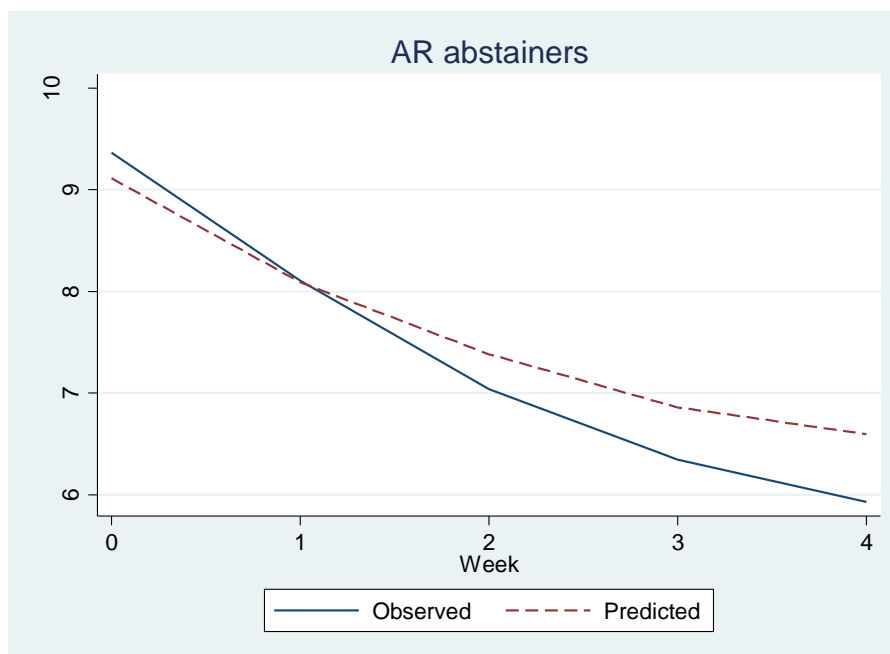
0.0 %

05/09 12/09 19/09

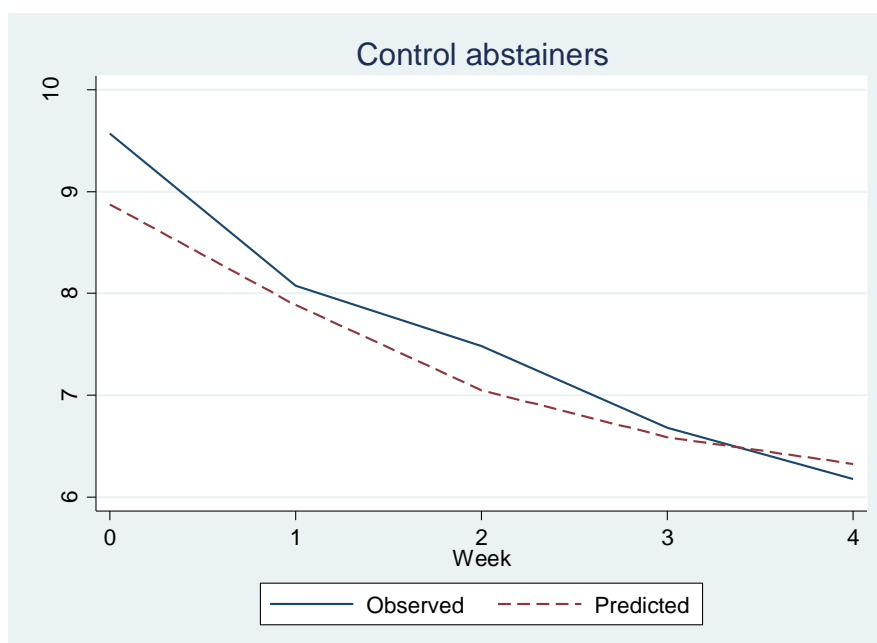
Close

**Appendix 26. Observed and predicted MPSS-C scores over time in each trial arm and by abstinence status**

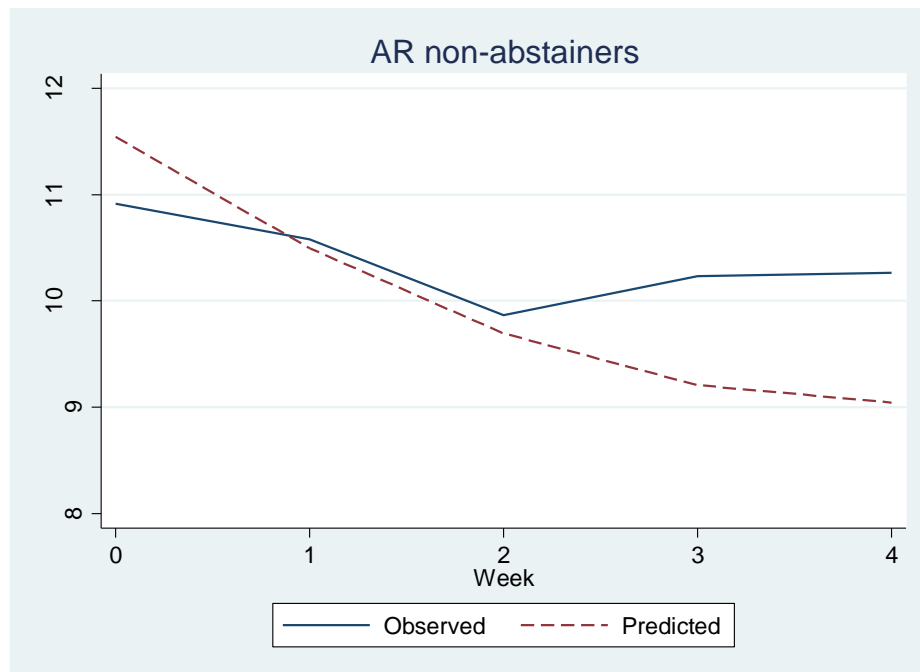
*a) Observed and predicted MPSS-C scores in attentional retraining group abstainers*



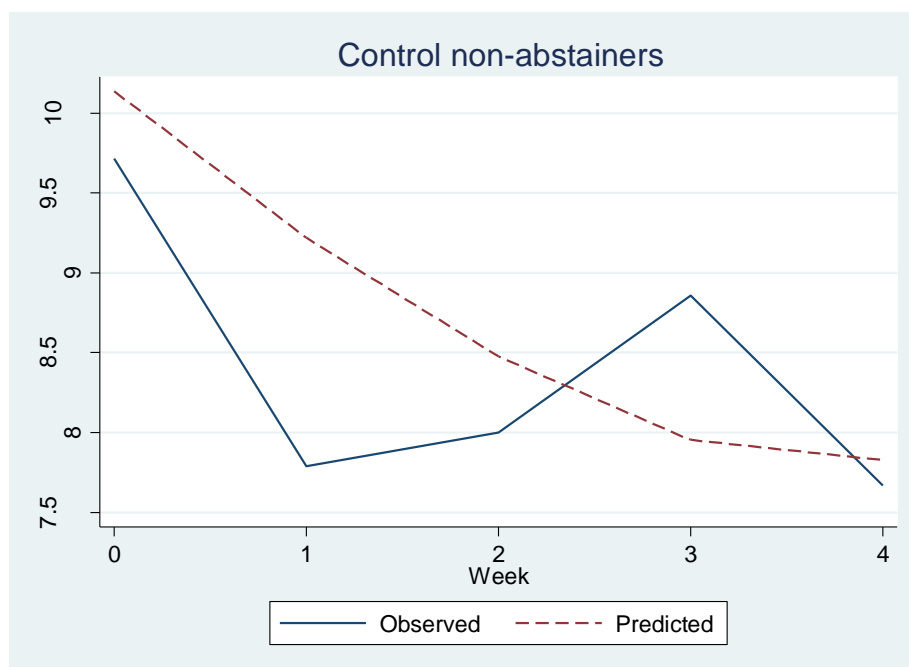
*b) Observed and predicted MPSS-C scores in control group abstainers*



- c) *Observed and predicted MPSS-C scores in attentional retraining group non-abstainers*

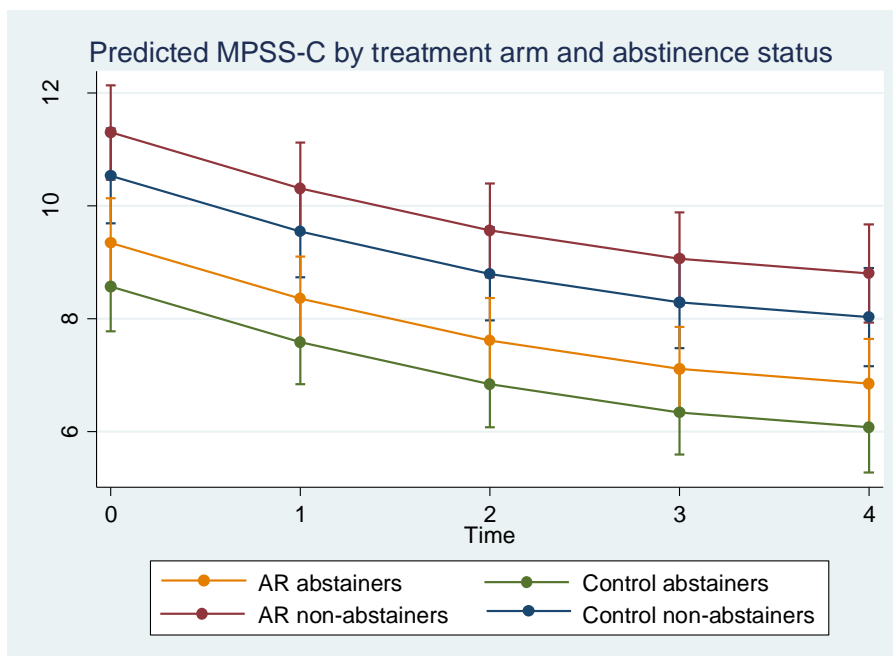


- d) *Observed and predicted MPSS-C scores in control group non-abstainers*

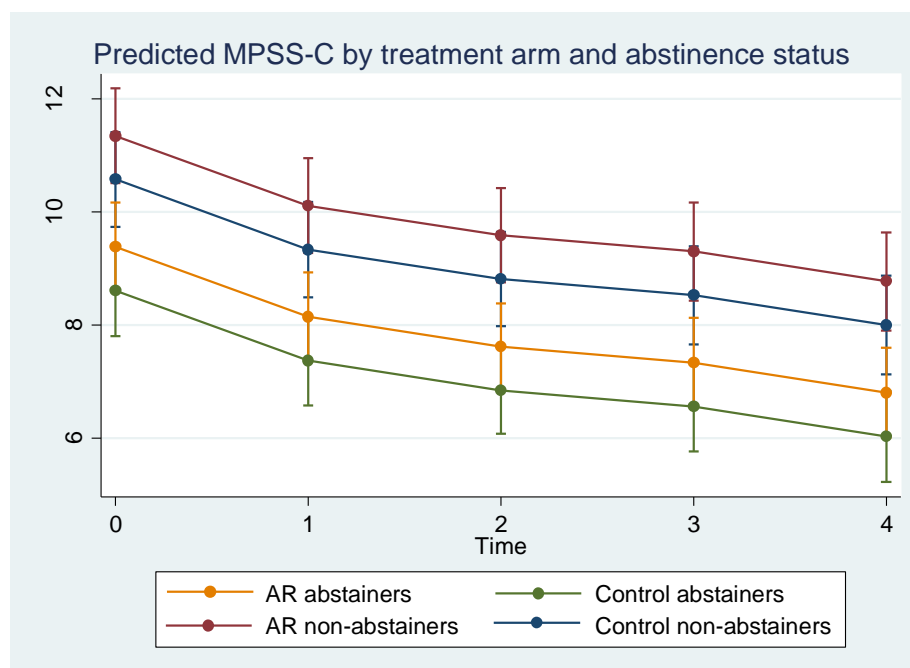


**Appendix 27. Predicted MPSS-C scores over time by trial arm and abstinence status (for fixed part of model only)**

a) *Predicted MPSS-C scores with main effects of time, time squared, trial arm and abstinence status*



b) *Predicted MPSS-C scores with main effects of time, time squared, time cubed trial arm and abstinence status*



**Appendix 28. Mixed-effects models of MPSS-C scores over time by trial arm and weekly abstinence status**

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects										
Time	0.91	0.50	-1.39	0.01	-1.30	0.01	-1.28	0.01	-1.22	0.01
Time <sup>2</sup>	-0.17	0.34	0.13	0.02	0.13	0.02	0.13	0.02	0.13	0.02
Treatment arm <sub>1</sub>	2.89	0.38	-0.32	0.80	0.52	0.55	0.32	0.68	0.71	0.11
Abstinence status <sub>2</sub>	5.13	0.06	0.37	0.70	0.94	0.22	0.79	0.27	0.77	0.28
Intercept	8.48		12.18		11.84		11.89		11.70	
Interactions										
Time x Abstinence status	-3.34	0.03	-0.45	0.06	-0.60	0.001	-0.60	0.001	-0.60	0.001
Time x Treatment arm	-1.67	0.38	0.34	0.26	0.12	0.52	0.10	0.54		
Treatment arm x Abstinence status	-2.98	0.44	0.88	0.54	-0.31	0.61				
Time x Treatment arm x Abstinence status	2.04	0.35	-0.33	0.35						
Time <sup>2</sup> x Abstinence status	0.37	0.06								
Time <sup>2</sup> x Treatment arm	0.26	0.27								
Time <sup>2</sup> x Treatment arm x Abstinence status	-0.30	0.27								
Random effects										
Participant ID, intercept (SD)	1.70		1.71		1.71		1.73		1.72	
-2*log likelihood	-1038.18		-1039.97		-1040.40		-1040.53		-1040.72	

Model 1: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status

Model 2: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x treatment arm, time x abstinence status, time x treatment arm x abstinence status

Model 3: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm

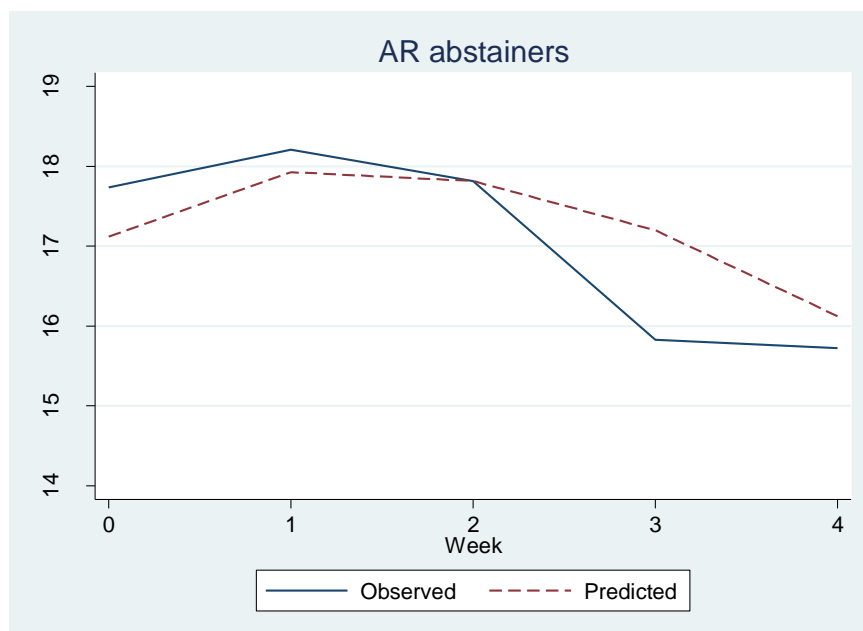
Model 4: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms time x abstinence status, time x treatment arm

Model 5: craving score by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms time x abstinence status

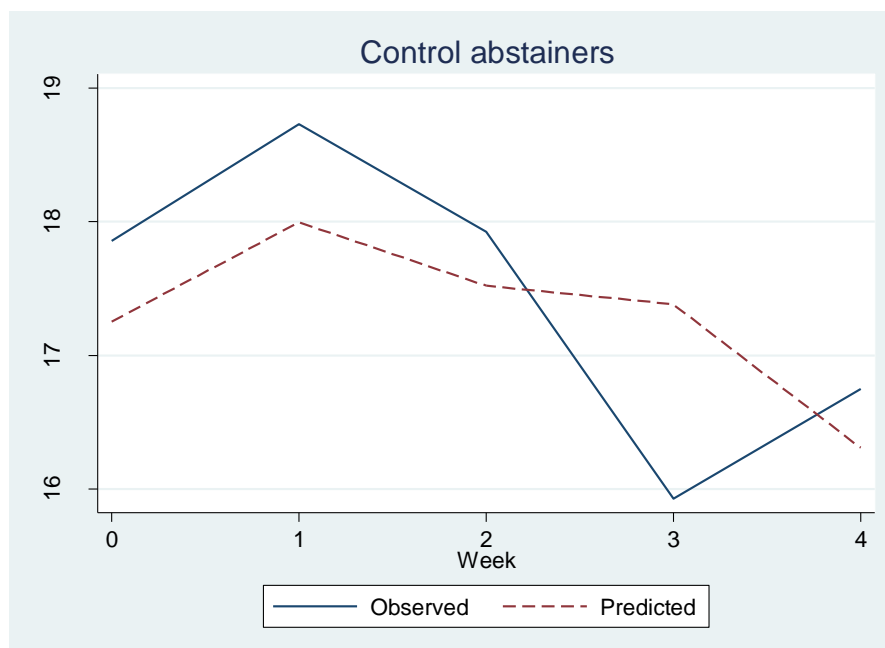
<sub>1</sub> Reference category is control group, <sub>2</sub>Reference category is non-abstainers

**Appendix 29. Observed and predicted MPSS-M scores over time in each trial arm and by abstinence status**

*a) Observed and predicted MPSS-M scores in attentional retraining group abstainers*

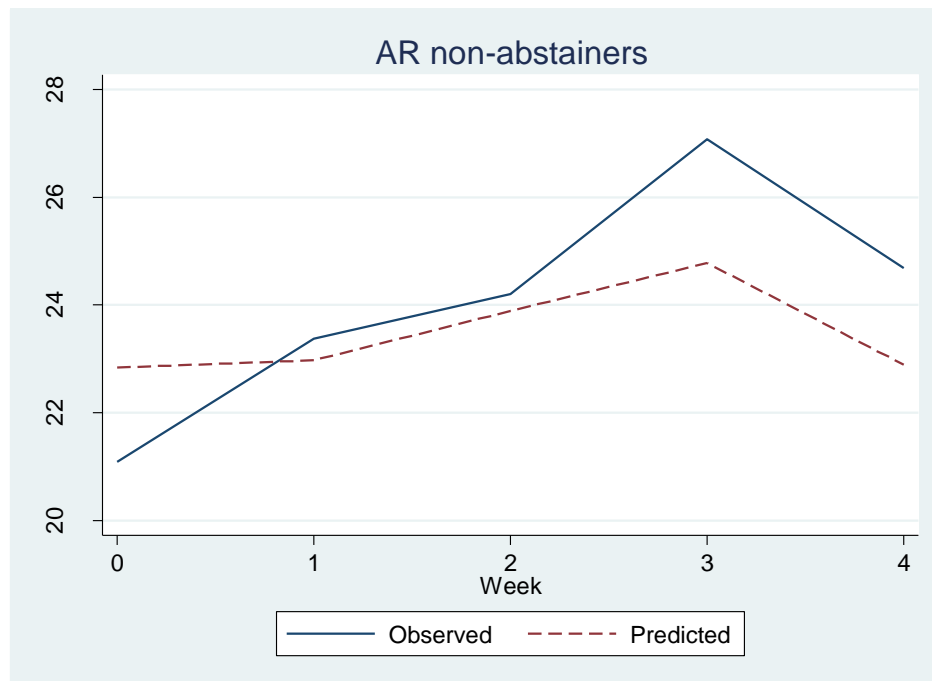


*b) Observed and predicted MPSS-M scores in control group abstainers*

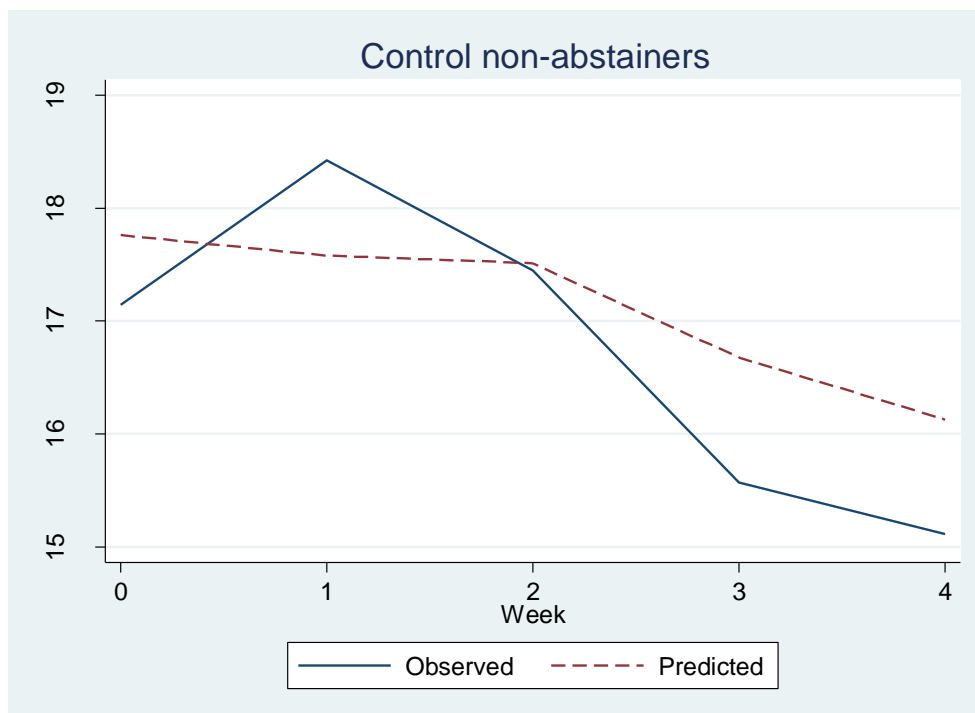




- c) *Observed and predicted MPSS-M scores in attentional retraining group non-abstainers*

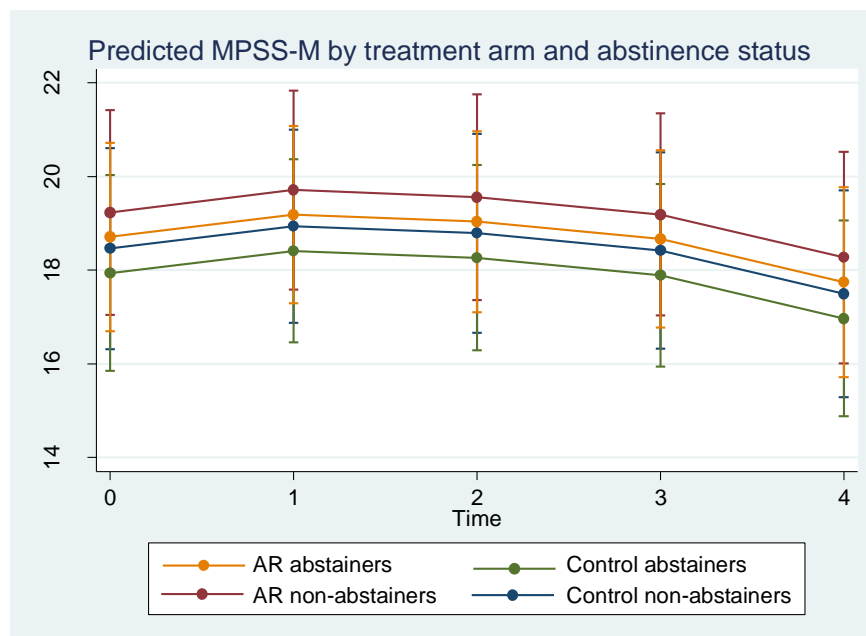


- d) *Observed and predicted MPSS-M scores in control group non-abstainers*

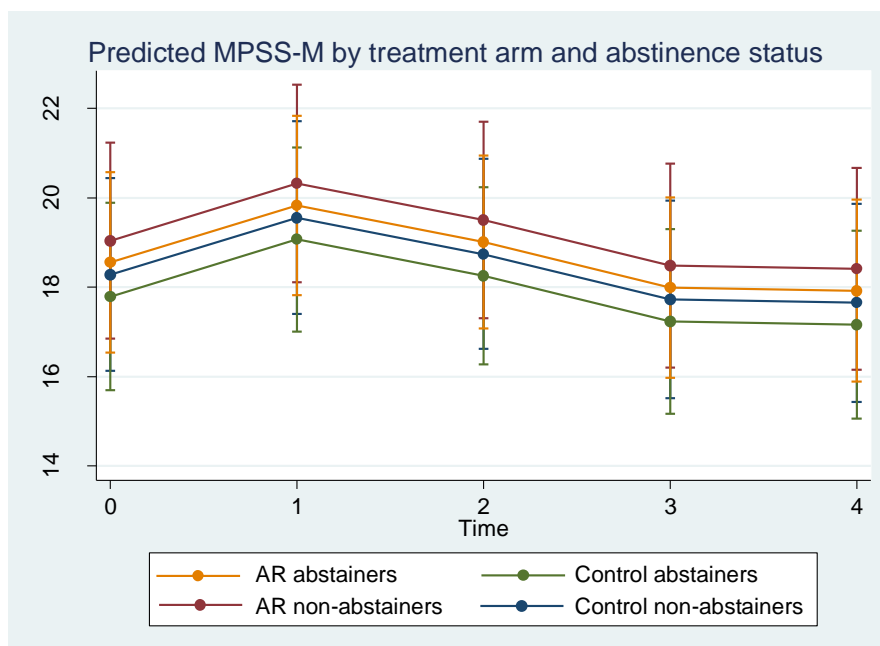


### Appendix 30. Predicted MPSS-M scores over time by trial arm and abstinence status (for fixed part of model only)

a) *Predicted MPSS-M scores with main effects of time, time squared, trial arm and abstinence status*



b) *Predicted MPSS-M scores with main effects of time, time squared, time cubed trial arm and abstinence status*



### Appendix 31. Mixed-effects models of change in VAS craving scores over time by trial arm and abstinence status

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Variable	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p	Regression coefficient	p
Fixed effects												
Time	-0.80	0.56	-1.46	0.04	-1.18	0.08	-1.15	0.08	-1.36	0.03	-1.36	0.03
Time <sup>2</sup>	0.03	0.74	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.08	0.07	0.08
Treatment arm <sub>1</sub>	-8.36	0.14	-8.17	0.08	-4.85	0.24	-4.54	0.21	-4.64	0.20	-0.23	0.93
Abstinence status <sub>2</sub>	2.90	0.61	0.51	0.92	3.79	0.36	3.75	0.37	1.17	0.74	5.21	0.04
Intercept	5.54		6.62		4.95		4.80		6.11		3.90	
Interactions												
Treatment arm x Abstinence status	13.82	0.08	14.34	0.03	7.87	0.11	7.94	0.10	8.05	0.10		
Time x Abstinence status	-1.21	0.50	0.10	0.84	-0.39	0.25	-0.39	0.25				
Time x Treatment arm	0.74	0.70	0.61	0.23	0.05	0.88						
Time x Treatment arm x Abstinence status	-0.77	0.76	-1.00	0.14								
Time <sup>2</sup> x Abstinence status	0.09	0.45										
Time <sup>2</sup> x Treatment arm	-0.01	0.94										
Time <sup>2</sup> x Treatment arm x Abstinence status	-0.01	0.93										
Random effects												
Participant ID, intercept (SD)	9.03		8.96		8.73		8.72		8.52		8.81	
-2*log likelihood	-1598.56		-1599.06		-1600.12		-1600.13		-1600.77		-1602.10	

Model 1: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status, time<sup>2</sup> x abstinence status, time<sup>2</sup> x treatment arm, time<sup>2</sup> x treatment arm x abstinence status

Model 2: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm, time x treatment arm x abstinence status

Model 3: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status, time x treatment arm

Model 4: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status, time x abstinence status

Model 5: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status and interaction terms treatment arm x abstinence status

Model 6: VAS difference scores by time, time<sup>2</sup>, treatment arm, abstinence status

<sub>1</sub> Reference category is attentional retraining group, <sub>2</sub> Reference category is abstainers